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Editorial

Monoclonal antibodies in corneal transplantation

Monoclonal antibodies are highly specific and powerful reagents which have proved invaluable in mapping the distribution and dissecting the function of cell-surface antigens, especially on cells of the immune system, and are finding an increasing use in clinical medicine.[1] The murine anti-CD3 monoclonal antibody known as OKT3, with specificity for a cell-surface antigen found on T-lymphocytes, is widely used to reverse corticosteroid-resistant renal allograft rejection episodes and a variety of other antibodies are currently under trial in clinical transplantation studies. Murine monoclonal antibodies directed against human T-cells have already been used as adjuncts to topical corticosteroids in attempts to reverse clinical corneal graft rejection.[2,3]

As well as having actual or potential uses as immunosuppressive agents in transplantation, monoclonal antibodies can help biologists to understand the underlying mechanisms of graft rejection. One of the more interesting areas of current research concerns the nature of the T-cell that is involved in graft rejection. CD4-positive T-cells, restricted by major histocompatibility complex (MHC) class II antigens, are predominantly involved in helper cell and delayed-type hypersensitivity (DTH) responses, whereas CD8-positive T-cells, restricted by MHC class I antigens, are predominantly involved in cytotoxic cell and suppressor cell responses. The type of T-cell that will accumulate in a rejecting graft is likely to depend to some extent on the type of MHC antigen disparity between donor and host, and both CD4- and CD8-positive T-cells have been observed in rejecting corneal grafts. However, identification of the major subset of T-cells accumulating in mismatched grafts should allow therapy directed against specific effector cells to be targeted more precisely.

In a paper published in this issue of the journal, Ayliffe and colleagues have demonstrated that euthymic rats, chronically depleted of CD4-positive cells by multiple intraperitoneal injections of monoclonal antibody prior to graft, show significant prolongation of orthotopic corneal graft survival when compared with control animals treated with monoclonal antibody of irrelevant specificity. A small number of grafts survived indefinitely in the anti-CD4-treated rats. Depletion of CD8-positive cells, in contrast, had no effect on corneal graft survival in a separate group of animals. The authors suggest that CD8-positive cells are not important in corneal allograft rejection but that CD4-positive cells may play a critical role. In an outbred model of orthotopic corneal transplantation in the rabbit, it has recently been shown that the cells infiltrating unmodified, rejecting grafts are heterogeneous, but contain a substantial proportion of granulocytes and macrophages indicative, perhaps, of a DTH-like response.[4]

The graft survival data reported by Ayliffe *et al* are similar to those recently obtained in a mouse model of orthotopic corneal transplantation by He *et al*,[5] in which intraperitoneal injections of monoclonal antibody to CD4 but not to CD8, given on four occasions, were found to prolong orthotopic corneal graft survival across a major MHC mismatch in adult thymectomised mice. Duguid *et al* have shown that an antibody to CD4 will prolong the survival of human corneal xenografts transplanted heterotopically to the subcapsular renal space in the mouse.[6]

Recent experimental studies in a variety of transplantation systems have suggested that a short course of monoclonal antibody therapy, given systemically in the perioperative period, can prolong graft survival and can induce a form of specific transplantation tolerance in some animals.[7] The most promising studies have involved the use of anti-CD4 antibodies,[8] though useful results have also been obtained with antibodies to other determinants. The ability to induce specific donor non-responsiveness in the recipient of a corneal graft is a long standing goal of many clinicians. This goal may never be met but it seems possible that the use of monoclonal antibodies may at least provide useful, specific immunosuppressive agents to reduce the incidence of rejection in high risk recipients and to reverse otherwise intractable rejection episodes.

K A WILLIAMS
D J COSTER

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British Journal of Ophthalmology 1992; **76**: 578–581

ORIGINAL ARTICLES

The red eye of renal failure: a crystal induced inflammation?

N Klaassen-Broekema, O P van Bijsterveld

Abstract

Of 57 patients with chronic renal failure and calcification of the anterior membranes of the eye eight developed inflammatory reactions, clinically indistinguishable from pingueculitis. In three patients an acute inflammatory reaction of the episcleral tissue and the conjunctiva over it developed which we considered to represent the red eye *of* renal failure. In these patients massive shedding of calcium phosphate salts was clinically evident. Histopathologically in all these patients calcific deposits were observed. Although sporadically polymorphonuclear leucocytes were present in the inflamed tissues we could not demonstrate crystal phagocytosis. We believe that in the red eyes *in* renal failure and, more specifically, in the red eyes *of* renal failure a crystal induced inflammatory mechanism is not operative.

(*Br J Ophthalmol* 1992; **76**: 578–581)

In patients with renal failure requiring regular haemodialysis, calcific deposits in the conjunctiva and cornea are common. As calcium phosphate salts are sparingly soluble and, as for the precipitation of the salt, the product of the concentration of the positively and negatively charged part of the salt is constant, an increase in either serum calcium or serum phosphorus concentration, large enough to exceed the in vivo solubility product, will lead to the deposition of calcium phosphate salts in the form of microcrystalline hydroxyapatite.[1]

An acute inflammatory response in the joints associated with the presence and phagocytosis of urate crystals has been described.[2] Hydroxyapatite crystals also have a marked phlogistic potential.[3] After being ingested by polymorphonuclear leucocytes they lead to cell death and to the release of large quantities of enzymes all capable of initiating inflammatory reactions. The crystals extruded in the extracellular tissue set in motion a new cycle of phagocytosis, cell death, and the release of inflammatory mediators continuing the inflammatory response.[4]

Berlyne[5] formulated the skilful theory of crystal induced inflammation, a dose related and reversible inflammatory reaction,[6] for the explanation of the mechanism of the red eyes of renal failure. The histopathological study of Berlyne demonstrated the presence of subconjunctival polymorphonuclear leucocytes and calcium phosphate crystals small enough to be phagocytosed, a prerequisite for the crystal induced inflammation theory. However, no mention was made of phagocytosis and he did not pursue the crystal induced inflammation concept to explain the red eyes in renal failure.

Berlyne and Shaw[7] took a conjunctival biopsy of a patient they considered to present with the red eye in renal failure. However their biopsy may have been taken from an inflamed pinguecula as demonstrated by the figure shown in their report. We therefore studied biopsies from patients with a distinctly different type of inflammatory reaction, clinically characterised by a waxy-red hyperaemia of the episclera and the conjunctiva over it, patients who were biochemically characterised by a high calcium/phosphorus ratio.[8] In addition we examined biopsies that were taken from patients without any inflammatory reactions of the outer membranes of the eye and also from patients with inflammatory reactions clinically indistinguishable from pingueculitis.

Patients and methods

The patient groups were identified both clinically and biochemically: group A consisted of 46 patients with calcium deposits but without the occurrence of an inflammatory reaction during the observation period, which was 6 years on average. Group B consisted of eight patients with calcification and inflammatory reactions associated with pingueculae. We considered these patients to represent the red eyes *in* renal failure. Group C consisted of three patients with an inflammatory reaction resembling diffuse episcleritis, extending well beyond the palpebral aperture, and an associated conjunctivitis which we considered the red eye *of* renal failure. Biochemically these patient groups were characterised on the basis of the relationship between the serum calcium and phosphorus concentration. Fifty healthy persons, matched in sex and comparable in age and weight, were used as controls.

Conjunctival biopsies were taken from patients of the three main groups and were examined by light microscopy. The tissues were fixed in phosphate buffered neutral formalin (10%). The histological sections were processed according to standard methods. The histochemical stains used were haematoxylin and eosin, to reveal the general cell structure, Giemsa stain and toluidine blue for the study of

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Table 1 The average calcium/phosphorus product and the number of persons in groups A, B, C, and the control group (Co) are shown with the standard deviations

	Group			
	A	B	C	Co
Average	4·59	5·02	6·62	3·13
Number	46	8	3	50
SD (n−1)	1·29	1·41	1·62	0·46

Table 2 The average serum calcium/phosphorus ratio, the number of patients and the standard deviation in patients of groups A, B, C, and the control group (Co)

	Group			
	A	B	C	Co
Average	1·51	1·44	2·00	1·90
Number	46	8	3	50
SD (n−1)	0·56	0·39	0·75	0·24

polymorphonuclear leucocytes. The van Gieson stain was used to study degeneration of connective tissue. Calcium deposits were shown by the von Kóssa stain. Fresh tissue biopsies were taken and examined with immunofluorescence techniques to reveal tissue complement activation.

Results

Serum calcium and phosphorus product

In Table 1 the average values of the serum calcium-phosphorus product of patient groups A, B, C, and the control group are shown. Statistically there was a significant difference between the patient groups and the control group. The patient groups all showed higher values than the control group. This is shown graphically in Figure 1. From this figure it is apparent that between the patient groups there was also a difference; statistically this difference was significant.

The highest calcium phosphorus product was observed in patients of group C. These patients had inflammatory reactions characterised by a diffuse waxy red episcleral and conjunctival hyperaemia. However in this group the average value of the serum calcium-phosphorus product exceeded the empirically observed serum calcium-phosphorus product value that, in the past, was associated with the red eye of renal failure.[7]

Table 3 Percentage increase of the serum calcium and serum phosphorus concentration in patients of groups A, B, and C in comparison with these values of the control group

	Group		
	A	B	C
Calcium	3·2	7·7	31·7
Phosphorus	30·0	32·6	32·6

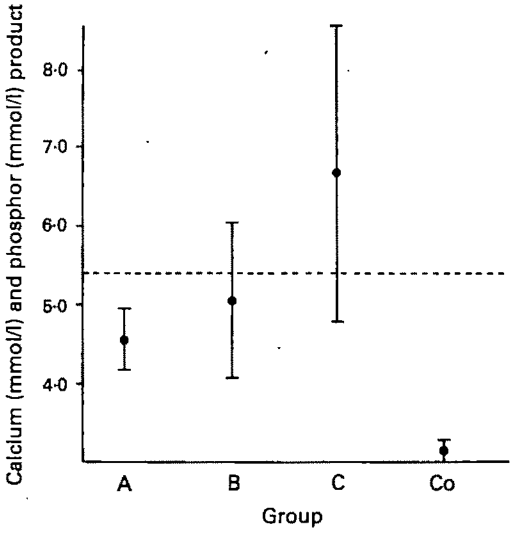

Figure 1 The average serum calcium (mmol/l) and phosphorus (mmol/l) product, with 95% confidence interval, of 46 patients (A) with calcific deposits but without inflammatory reactions, of eight patients (B) associated with pingueculae, and of three patients (C) characterised by a waxy red diffuse episcleral inflammatory reaction and the conjunctiva over it, extending well beyond the palpebral fissure, at the height of the inflammatory reaction. The calcium phosphorus product of the control group (Co) is also shown. The broken line shows the empirical calcium-phosphorus product above which the red eyes in renal failure were said to be associated.

Serum calcium/phosphorus ratio

In Table 2 the average serum calcium/phosphorus ratios are shown for the patient groups A, B, C, and the control group. The control group and group C had the highest value. There was a statistically significant difference in the serum calcium/phosphorus ratio between the patient groups and the control group but not among the patient groups. The inability to demonstrate a difference between group A and B on the one hand and group C on the other was the consequence of the smaller number of patients in group C. The difference between the patient groups we observed, however, was found to be dependent on the contribution of the average serum calcium concentration to the ratio; the serum phosphorus concentration was constant, as shown in Table 3.

Histopathology

A conjunctival biopsy of a representative patient from group A showed marked subepithelial calcium deposits. There was a certain amount of elastotic degenerated connective tissue. No inflammatory cells in or around the calcific deposits were observed, but perivascularly some polymorphonuclear leucocytes were seen. There was no distension of the conjunctival or episcleral vessels.

In the biopsies of patients from group B marked deposits of subepithelial calcium were also seen. The collagen fibres were degenerated. A localised, moderate increase in polymorphonuclear leucocyte infiltration was seen in almost half of the cases. Sporadic leucocytes were observed in 14% of the biopsies; however these inflammatory cells may be completely absent. No crystal phagocytosis of calcific material was observed. The histopathology of this group is compatible with that of pingueculitis.

In the biopsies of patients of group C both conjunctival and episcleral vessels were markedly dilated. There was a marked degree of elastotic degeneration of collagen fibres. Calcium salts were present subepithelially. A few degranulating mast cells near the calcium deposits were observed. A moderate inflammatory reaction was shown in all patients, characterised by pavementing of the endothelium of the vascular walls by polymorphonuclear leucocytes; these cells were also visible perivascularly. A few eosinophilic cells, lymphocytes, and plasma cells were among the inflammatory cells. The inflammatory reaction was diffuse and nongranulomatous (Fig 2). Polymorphonuclear cells

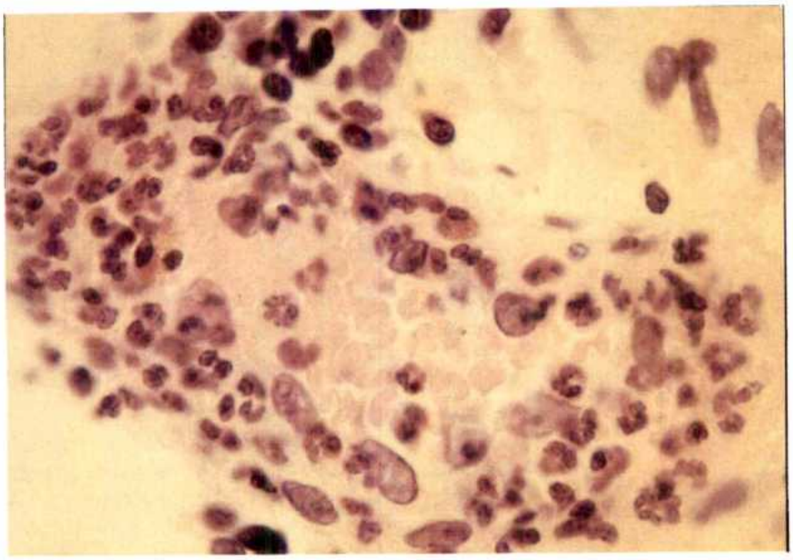

Figure 2 Histopathology of a conjunctival biopsy of a patient from group C, clinically characterised by a waxy red episcleral hyperaemia extending beyond the palpebral aperture. Pavementing of the endothelium by polymorphonuclear leucocytes of the vascular wall is shown. Also visible are lymphocytes, eosinophilic cells, plasma cells, as well as perivascular infiltration of leucocytes. Haematoxylin and eosin, ×900.

were not located in the areas of calcification (Fig 3). No crystal phagocytosis was observed. The histopathology of this group is compatible with primary, simple episcleritis. No complement activation was detected by immunofluorescence.

Discussion

After being phagocytosed microcrystalline hydroxyapatite is very toxic to leucocytes[9] because these crystals are membranolytic. It is therefore not surprising that for Berlyne the development of the red eye in renal failure is none other than the mechanism of crystal induced arthritis. He looked at the conjunctival sac as a specialised joint in which the moving surfaces are the lids and eyeball; the conjunctiva being analogous to the synovial membrane. The presence of polymorphonuclear cells, mononuclear cells, as well as crystals small enough to be phagocytosed, being the conditions for the induction of a crystal induced inflammation, seems to favour such a mechanism.

Hydroxyapatite crystal deposition in soft tissues will occur when the serum concentrations of calcium and phosphate exceed the solubility product – that is, in a marked supersaturated solution. In vitro the serum calcium/phosphorus ratio determines the type of salt formed. In a high calcium/phosphorus ratio of 1·67 or more, salts are deposited in a crystalline form, while a low ratio results in amorphous deposits.

If the concentration of calcium and phosphorus ions increase homogeneically, large crystals are formed; small crystals are deposited if the ion concentrations increase inhomogeneically. In a situation that favours the precipitation of calcium salts of a crystalline nature, and in view of the pathophysiology of renal failure one can expect the deposition of predominantly microcrystalline deposits of hydroxyapatite, which was demonstrated.[5]

Particularly in the rather acute and pronounced diffuse episcleral and conjunctival inflammatory reactions of the patients of group C, the average serum calcium/phosphorus ratio was 2·00, the result of the rather marked increase of the serum calcium concentration. Here, one can expect massive shedding of crystals, which we observed clinically, one of the prerequisites of crystal induced inflammation.

Hydroxyapatite crystals, most of which are less than 0·5 μm long, cannot be seen by light microscopy and crystal phagocytosis could be difficult to demonstrate in a routine histopathological examination. Hydroxyapatite crystals have, however, a marked tendency to clump and to arrange themselves within a connective tissue matrix.[10 11] These clumps of crystal and matrix can be seen by light microscopy, free or intraleucocytic, as in periarthritis.

In spite of the presence of subconjunctival extracellular hydroxyapatite crystals in an acutely inflamed episcleral and conjunctival tissue, we were not able to observe crystal phagocytosis. In group C and also in the majority of the patients in group B there is an increased polymorphonuclear leucocyte infiltration, but they are not in the vicinity of calcific deposits. We did not observe chemotaxis exerted by hydroxyapatite crystals in the conjunctiva.

The absence of crystal induced phagocytosis in the presence of hydroxyapatite crystals suggests a 'switch-off' phenomenon. Phagocytosis of crystals is expedited when certain proteins are adsorbed to the surface of the crystal[12] and inhibited if crystals are coated by competing proteins. One can hypothesise that the absence of phlogistic activity of the hydroxyapatite crystals in the red eye of renal failure might be related to adsorbed molecules such as hyaluronate[13] or glycoproteins.[14] Adaptation to crystals manifested clinically by their silent presence might be explained by such a mechanism.

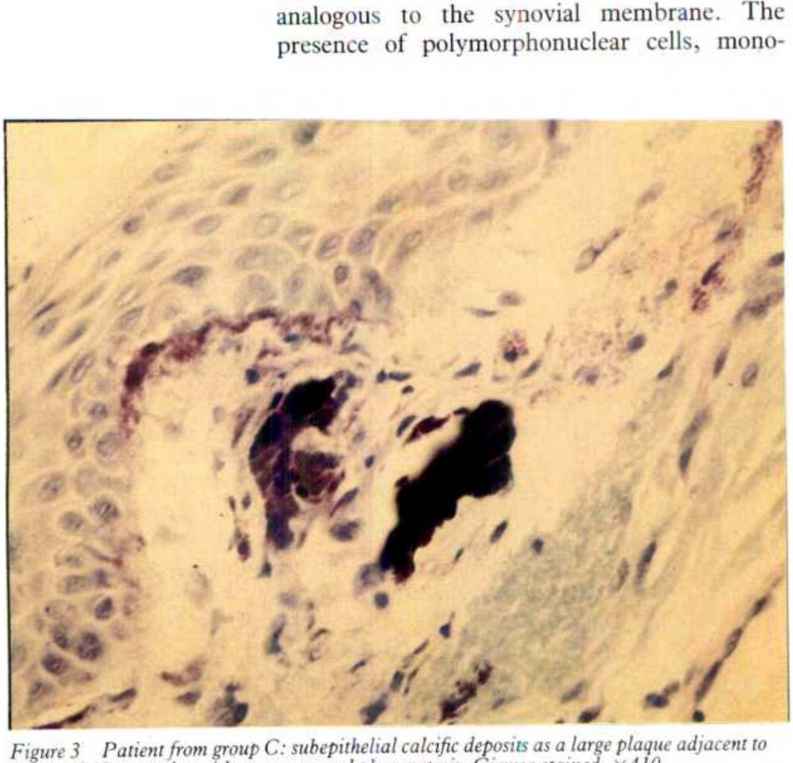

Figure 3 Patient from group C: subepithelial calcific deposits as a large plaque adjacent to small calcific granules without any crystal phagocytosis. Giemsa stained, ×410.

We are grateful to Dr A Hamburg for the interpretation of the histopathological slides.

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British Journal of Ophthalmology 1992; 76: 582–585

Herpetic keratitis in Tanzania: association with malaria

David Yorston, Allen Foster

Abstract

Of 103 patients who presented to a rural clinic in Africa with corneal ulceration, 62 (60·2%) had corneal ulcers which on clinical diagnosis were attributable to herpes simplex virus. There was a strong association between herpetic ulceration and a history of recent malaria; 37 of 62 (59·7%) herpetic ulcers occurred in the 3 month period from April to June which corresponds to the end of the peak season for malaria compared with 14 of 41 (34%) of the non-herpetic ulcers. Fifty per cent of herpetic ulcers had a geographic morphology, 27·4% were dendritic, and 22·6% presumed herpetic ulcers were stromal: 38·7% of herpetic ulcers occurred in children under 5 years of age. Bilateral herpetic ulcers occurred in 16·1% of patients but were more common in children under 2 years of age. Geographic and stromal ulcers tended to heal more slowly than dendritic ulcers (mean time to healing 12·6, 12·2, and 6·6 days respectively), and were more likely to result in severe corneal scarring (45%, 29%, and 0% respectively). Herpes simplex keratitis is a major cause of corneal scarring in Africa. It is often seen in children, may be bilateral, commonly is geographic in morphology, and has a strong association with malaria infection. Because it is not easily preventable, more effort must be made to ensure early diagnosis and prompt, effective treatment in order to prevent severe scarring and visual loss.

(*Br J Ophthalmol* 1992; **76**: 582–585)

It has been known for over a decade that herpes simplex virus (HSV) type 1 can produce severe corneal ulceration in children in both west and east Africa, particularly in relation to measles[1-3]; however there have been few reports of herpetic ulceration in adults.

In industrialised countries the commonest form of HSV ulcer is the dendritic pattern, in which viral replication is confined to the epithelium, and which usually heals with little or no corneal scarring. Geographic and stromal ulcers do occur, most commonly in immunosuppressed patients, or following the inappropriate use of topical steroids.[4] In Africa, severe geographic or stromal ulceration which is presumed to be due to HSV, on account of its morphological appearance and response to specific antiviral therapy, appears to be the norm rather than the exception. As a result, HSV keratitis is even more important as a cause of ocular morbidity and visual loss in Africa than in developed countries. This study was undertaken in order to investigate the characteristics of corneal ulcers presumed to be caused by HSV in Tanzania.

Methods

A prospective study evaluated all patients presenting to the Mvumi Hospital eye clinic between April 1988 and March 1989 inclusive. Mvumi hospital is a mission hospital situated 40 km south east of Dodoma in the centre of Tanzania. The area is arid and infertile, and is known as one of the poorest regions of the country. The rains occur from January to April, and are associated with a seasonal malaria epidemic. Trachoma and bacterial conjunctivitis are very common.

Patients presenting with corneal ulceration were examined by one ophthalmologist (DY). Details were recorded, including information regarding any recent episode of malaria, or use of traditional eye medicines (TEM) within the previous 2 weeks. The patients underwent ocular examination, including slit-lamp biomicroscopy. Corneal ulcers were drawn and photographed. The patients were admitted and treated appropriately according to the clinical diagnosis.

The diagnosis was made on clinical grounds as laboratory confirmation was not possible in this setting. Patients with clinical HSV keratitis were categorised, depending on the predominant morphology of their ulcers, as having dendritic, geographic, or stromal ulceration (Figs 1, 2, 3). The clinical characteristics and morphological appearances of laboratory proved herpetic ulceration have been previously reported.[1-4] Patients with HSV keratitis were treated with idoxuridine (IDU) ointment five times per day, and atropine drops every 8 hours. Topical and subconjunctival antibiotics were only given if there was evidence of secondary bacterial infection, such as a hypopyon or purulent discharge. The response to specific treatment with

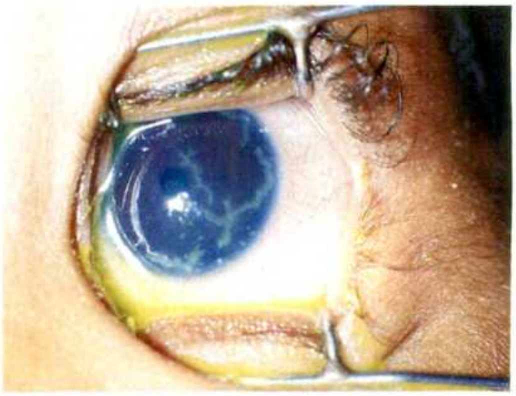

Figure 1 Dendritic type corneal ulceration.

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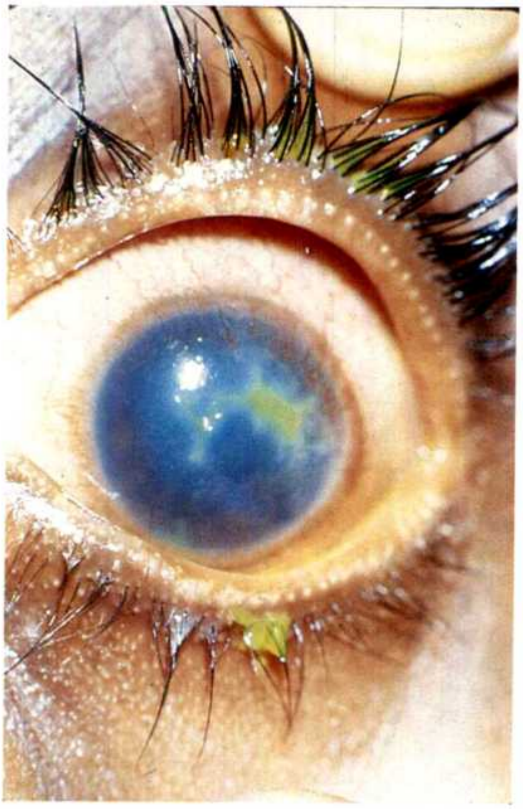

Figure 2 Geographic type corneal ulceration with vascularisation and stromal oedema.

idoxuridine ointment was also used to confirm the diagnosis of clinical herpetic keratitis (Figs 3 and 4). The patients remained in hospital and were examined daily until their ulcers healed. The time to healing, defined as 'no corneal staining with fluorescein', was recorded for all ulcers.

The outcome of the ulceration was graded according to the severity of corneal scarring at discharge: grade A – no or slight scarring, defined as corneal opacity that did not obscure the underlying iris detail; grade B – moderate scarring – a corneal opacity obscuring the iris detail but not in the visual axis; grade C – severe scarring, a corneal opacity in the visual axis which obscures the iris.

Results

Presumed HSV was responsible for 62 (60·2%, 95% confidence limit (CL) 50·6–69·8%) corneal ulcers in this study. Use of TEM can result in severe corneal ulceration and was directly responsible for 15% of all corneal ulcers in this study. It was also used in a further 10% of corneal ulcers due to other causes. (Table 1).

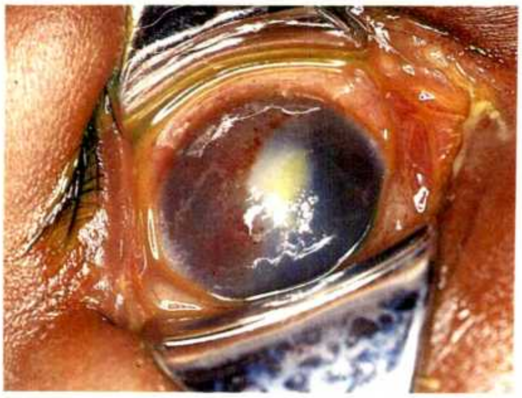

Figure 3 Stromal ulceration and severe vascularisation due to presumed herpetic keratitis.

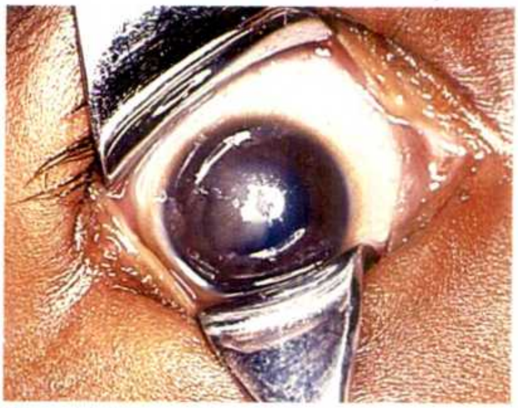

Figure 4 The same patient as in Figure 3 after 2 weeks of antiviral therapy with idoxuridine ointment five times per day.

Of the 62 ulcers attributed to herpes simplex 50% were geographic in morphology, 23% stromal (presumed herpetic) and 27% dendritic (Fig 5). Eight patients with herpetic ulceration gave a history of using TEM (13%), of whom five had an associated hypopyon.

Fifty four of 62 (87·1%) patients with herpetic ulceration gave a history of malaria in the preceding 2 weeks compared with nine of 41 (21·9%) patients with non-herpetic ulcers ($p<0·001$). A seasonal variation was noted with 37 of 62 (60%) of the herpetic corneal ulcers occurring in the 3 months from April to June, compared with 14 of 41 (34%) of the non herpetic ulcers ($p=0·01$) (Fig 6).

Twenty four of 62 (38·7%, 95% CL, 29·1%–48·3%) of the herpetic ulcers occurred in children aged 0–4 years and nine of 62 (14·5%) in children aged 5–10 years. A total of 54 of 62 (87·1%) occurred in patients under 30 years of age. In children aged 0–2 years seven of 19 (36·8%) herpetic ulcers were bilateral compared with three of 43 (7%) in all other age groups ($p=0·003$).

There was an excess of females (37: 25) in the herpetic group but this was not seen in non-herpetic ulcers (18:23), although this did not reach statistical significance ($p=0·12$). Five patients (8%) all aged under 2 years had associated herpetic skin ulcers.

The mean times to healing of the different morphological types of ulcers were geographic 12·6 days (95% CL, 10·0–15·2); stromal 12·2 days (95% CL, 6·2–18·2); and dendritic 6·6 days (95% CL, 5·3–7·9). The time taken to heal was not related to the age of the patient.

The outcome in patients with herpetic corneal ulcer was classified as minimal or no corneal scarring (A) in 40·3%; moderate scarring (B) in 30·6%; and severe scarring (C) in 29%. Severe scarring was a more frequent outcome in geographic ulcers (45·2%) and stromal ulcers (28%) than dendritic ulcers (0%) (Table 2).

Discussion

PREDISPOSING FACTORS FOR HERPETIC KERATITIS

Previously published reports have noted severe

Table 1 Aetiology of corneal ulceration in 103 patients, Mvumi, Tanzania

Cause	Unilateral		Bilateral		Total	
	n	%	n	%	n	%
Herpes simplex	52	61·8	10	52·6	62	60·3
Traditional eye medicines	15	17·9	0	0·0	15	14·6
Bacterial	7	8·3	2	10·5	9	8·7
Xerophthalmia	0	0·0	3	15·8	3	2·9
Mooren's ulcer	0	0·0	2	10·5	2	1·9
Trichiasis	2	2·4	0	0·0	2	1·9
Exposure	0	0·0	1	5·3	1	1·0
Other	5	6·0	1	5·3	6	5·8
Unknown	3	3·6	0	0·0	3	2·9
Total	84	100·0	19	100·0	103	100·0

herpetic ulcers in African children, often in relation to measles or malnutrition.[1-3] It has been suggested that both measles and malnutrition depress cell mediated immunity resulting in severe ulceration. This study confirms that severe herpetic corneal ulcers do occur, not only in children but also in adults living in east Africa.

Following an intensive immunisation campaign measles is now an uncommon disease in the area surrounding Mvumi Hospital,[5] and none of the cases of herpetic corneal ulceration seen during this study period of 12 months were related to measles infection.

Though some degree of malnutrition is widespread among children in this region, especially during weaning, significant degrees of protein-calorie malnutrition are uncommon among adults, except during serious famines. As a result the occurrence of severe HSV corneal ulceration in adults, as reported in this study, is unlikely to be attributable to either measles or malnutrition.

An increasingly common cause of immunodeficiency in Africa is infection with the human immunodeficiency virus (HIV). HIV serology was not performed on any of the patients included in this study. The two peaks in the incidence of herpetic ulcers, in children and in young adults, correspond to the populations known to be at greatest risk of HIV infection in Africa. Although no population based survey of HIV seropositivity has been carried out it was not thought to exceed 1% of the population in this rural part of Tanzania at the time of this study.

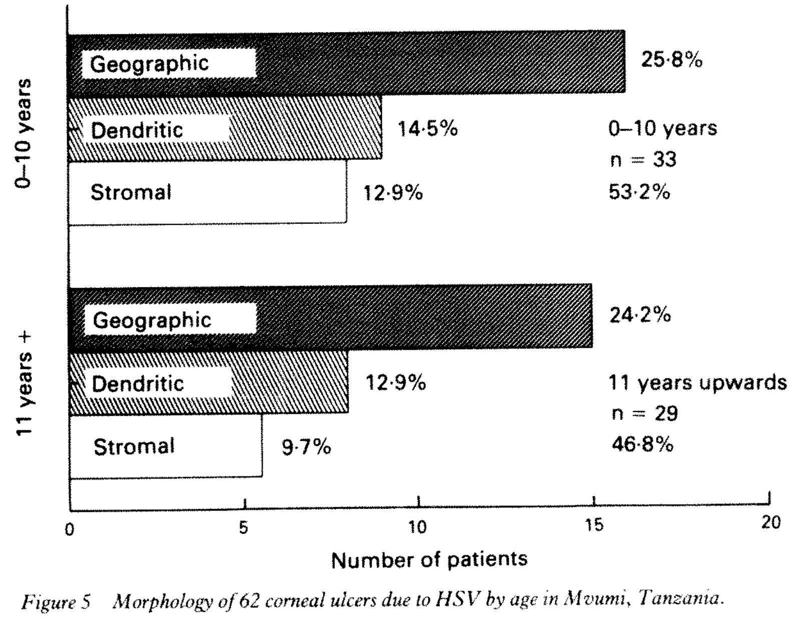

Figure 5 Morphology of 62 corneal ulcers due to HSV by age in Mvumi, Tanzania.

Topical steroids are not available outside the major towns in Tanzania, and are unlikely to be responsible for the severe HSV ulceration seen in these patients, almost all of whom came from small villages.

We have previously reported[6] that an increase in the incidence of malaria at Mvumi between February and May has been associated with an increase in the incidence of corneal ulcers in children attributable to HSV. This study confirms the seasonal increase in herpetic ulceration from April to June, which is not seen to the same extent with non-herpetic ulceration. This prospective study demonstrates an association between a history of recent malaria, and a diagnosis of herpetic corneal ulceration further giving support for the hypothesis that malaria is a major predisposing factor for herpetic keratitis in this area.

OUTCOME OF HERPETIC KERATITIS IN AFRICA

Although HSV ulcers are characteristically unilateral, in this study HSV was the commonest cause of bilateral ulceration, occurring in 10 out of 62 (16·1%) patients. Bilateral ulcers were more common in children under 2 years occurring in more than one third of those with herpetic ulcers. This may be related to nutrition which is more likely to be inadequate in young children.

Twenty nine percent of patients with herpetic ulceration developed scarring of a severity sufficient to reduce the visual acuity (grade C). Nearly half (45·2%) of patients with geographic ulcers had visually disabling scarring, affecting the central cornea. It has been estimated that half of all patients with HSV corneal ulcers will develop further recurrences within the following 2 years.[7] This suggests that in the years to come, many of the patients included will suffer a reduction in their visual acuity as a result of herpetic keratitis.

It has been shown that corneal scarring is the commonest cause of blindness in children in east Africa, occurring in 70% of children in blind schools.[8,9] As effective primary health care programmes succeed in reducing the incidence of corneal scarring from vitamin A deficiency and measles it is possible that herpetic keratitis will become the leading cause of visual loss owing to corneal ulceration in African children. Since corneal grafting is not yet feasible in most parts of the continent, strategies to reduce visual loss from HSV to a minimum should be identified.

PREVENTION AND MANAGEMENT OF HERPETIC KERATITIS IN AFRICA

Primary prevention of HSV infection is not yet possible, but research into possible vaccines continues. Avoidance of known precipitating factors, such as malaria, may have a role but prevention of malaria is not easy in rural African communities. Measles immunisation, and improved nutrition in young children, which are already included in most community health interventions, may prevent some episodes of HSV keratitis in children.

Secondary prevention through early and effective treatment with anti-virals would seem a

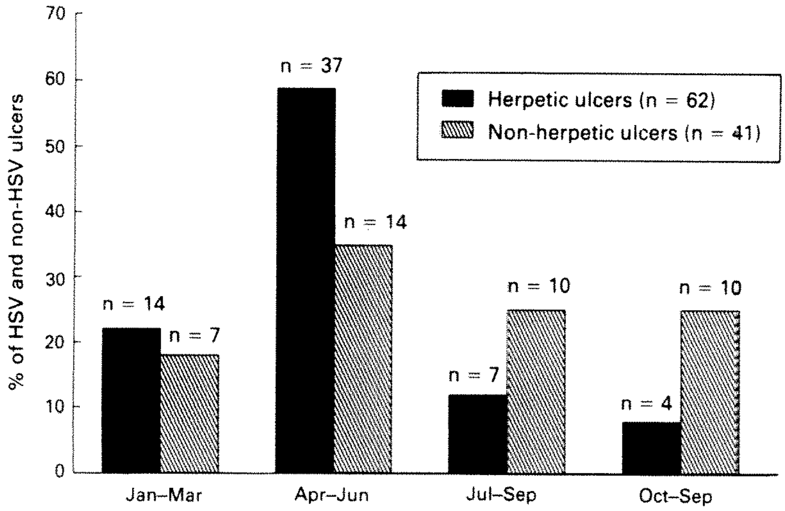

Figure 6 Corneal ulceration by cause and season in Mvumi, Tanzania.

reasonable possibility. This implies early diagnosis, which requires that the patient is examined promptly by an eye-trained medical worker. Unfortunately on average for every one million Africans there is only one ophthalmologist, and he or she is usually located in the large cities, out of reach of the rural population.[10] Training of more ophthalmic workers, at all levels, is a high priority for prevention of blindness in Africa.

Early diagnosis is of little benefit unless effective treatment is available and, unfortunately, local preparation of idoxuridine eye drops is difficult.[11] Idoxuridine ointment has toxic effects on the cornea and ocular surface if used for long periods, and costs about £1 for a 5 g tube. This is more than the per capita health budget of some African countries. Acyclovir has fewer adverse effects than idoxuridine, but is even more expensive. In Tanzania, idoxuridine ointment is only available at a few of the larger hospitals, which receive substantial support from foreign donor agencies. Mechanical debridement can be effective in the treatment of dendritic ulcers,[12] but is contraindicated in geographic and stromal ulceration. Mechanical debridement is also difficult to perform adequately in young children without resorting to general anaesthesia.

Table 2 Outcome in patients with herpetic corneal ulceration by morphology

Outcome	*Dendritic*		*Geographic*		*Stromal*		*Total*	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
A	16	94·1	8	25·8	1	7·1	25	40·3
B	1	5·9	9	29·0	9	64·3	19	30·6
C	0	0·0	14	45·2	4	28·6	18	29·1
	17		31		14		62	100·0

There is some laboratory work which suggests that povidone iodine 1% drops may be effective against HSV.[13] Povidone iodine is inexpensive, and a 1% drop can be made easily from the commercially available 10% solution.[11] Further work is in progress to evaluate PVI in the treatment of HSV corneal ulceration, and to assess any adverse effects of regular topical use.

Conclusion

Herpetic corneal ulcers are a common and serious cause of ocular morbidity in Africa. It is likely that malaria, malnutrition, measles, and late presentation are just some of the factors responsible for the aggressive pattern of disease seen in HSV corneal ulceration in Africa compared to Europe. At present, African patients with herpetic keratitis have little hope of receiving early or effective treatment. There is an urgent need for more eye-trained medical workers and for inexpensive, but effective, anti-herpetic drugs.

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Radial keratotomy: a review of 300 cases

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Abstract

Three hundred consecutive cases of radial keratotomy performed between 1985 and 1990 were reviewed. There were no sight threatening complications of surgery and no patient lost one or more lines of corrected Snellen acuity. Overall 78·7% saw 6/12 or better unaided postoperatively and 51·7% saw 6/6 or better. Refraction showed 61·3% to be within 1 dioptre of emmetropia and 86·7% were within 2 dioptres. Further analysis demonstrated that results of unaided acuity and proximity to emmetropia were much better for low (<−2·87 D) and moderate (−3·0 to −5·87 D) than for high (>−6·0 D) myopes.
(*Br J Ophthalmol* 1992; 76: 586–589)

Currently myopia is being treated by radial keratotomy and by photorefractive keratectomy using the excimer laser.[1,2] In order to assess the relative merits of these two techniques the results of radial keratotomy from one surgical team were reviewed over a period of 5 years.

Method

The notes were reviewed of 300 consecutive radial keratotomy procedures performed between 1985 and 1990 by one surgeon (AD McG S) or directly under his auspices.

Preoperative assessment involved a full ophthalmic examination including mydriasis for fundal examination, confirmation of a stable refraction, and pachymetry. Each patient was thoroughly counselled and the controversial and unpredictable nature of this form of surgery explained. Details of the possible early and late postoperative complications were provided.

All surgery was performed under general anaesthesia. The pupil was constricted preoperatively. The selected size of central clear zone was delineated with a corneal marker fitted with cross wires. Radial incisions were then made with a guarded knife set at 115% of the measured central corneal thickness. Incisions were made from the edge of the outer clear zone to the periphery, leaving a small margin of uncut cornea at the limbus. Four or eight incisions were utilised depending on degree of myopia. Finally the incisions were carefully irrigated with sterile saline, topical antibiotics were instilled, and the eye was padded.

Postoperatively all patients received prednisolone sodium drops 0·3% and chloramphenicol drops four times daily for 4 weeks. Patients were routinely reviewed at 2 and 6 weeks after surgery and then at 3, 6, 12, and 18 months.

Results

Three hundred procedures were performed on 169 patients of whom 100 were male. All were 21 years of age or older. The age of the patients at surgery is shown in Figure 1 and it may be seen that the majority fall within the 21–30 years age group. Mean time of follow-up was 19 months (range 12–60).

Reasons for wanting surgery are shown in Figure 2. All patients were referred for surgery either directly by their general practitioners (92·8%) or via other ophthalmologists (7·2%).

Peroperative complications included 35 cases of single perforation and nine cases in which there were two perforations. All but two were Seidel negative on the morning after surgery, and these were negative by the following morning.

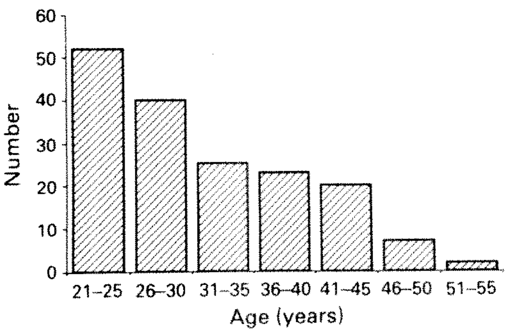

Figure 1 Age of patients at time of surgery.

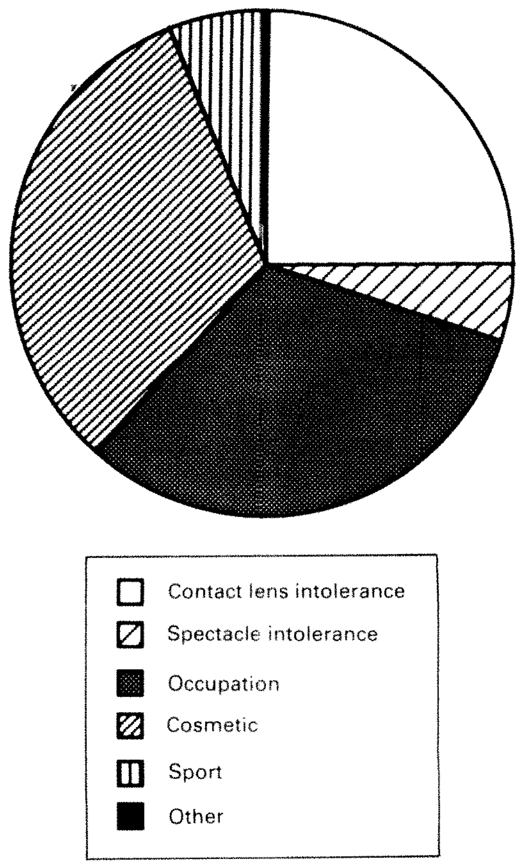

Figure 2 Reason given for wanting surgery.

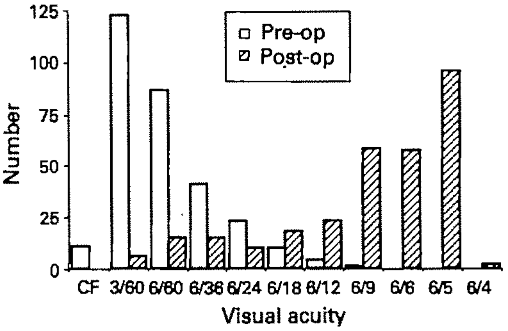

Figure 3 Unaided visual acuity before and after surgery – all patients.

Only one late postoperative complication was recorded; a patient who developed a giant retinal tear 3 months after uneventful surgery which was successfully treated. No other eye in the series lost one line of preoperative corrected Snellen acuity after surgery.

Figure 3 shows unaided Snellen visual acuity before and after surgery for all eyes. The values given here are from the patients' final follow-up visit and this is the case for all results unless otherwise stated. Expressed figuratively 78·7% of patients saw 6/12 or better unaided postoperatively and 51·7% saw 6/6 or better.

Spherical equivalent before and after surgery is shown in Figure 4. Expressed figuratively 61·3% patients were within 1 dioptre of emmetropia postoperatively and 86·7% were within 2 dioptres.

In order to highlight individual variation in response to surgery Figure 5 shows individual plots of pre- and postoperative refractions. The slope shows the no change line, with all those above the line having a reduction in myopia. This illustrates that the majority of patients with preoperative values of −2 to −6 dioptres achieve results close to emmetropia. Predictability appears to decline with increasing preoperative myopia. To attempt to examine this more closely, eyes were divided into three groups. Low myopes from 0 to −2·87 dioptres, moderate myopes from −3·00 to −5·87 dioptres, and high myopes of greater than −6·0 dioptres.

Firstly, postoperative unaided acuity is shown for the three groups in Figure 6. It is clear that predictability of outcome is much poorer in the higher myopes and is best in the low group. This is presented in Table 1 and shows the highest percentage of eyes achieving 6/12 and 6/6 in the low myopia group. The results are progressively poorer for the moderate and high myopia groups. This pattern is repeated with the results of postoperative refraction (Fig 7). The predictability of achieving a refractive result within 1 or 2 dioptres of emmetropia declines across these groups from 73·8% to 30·0% and from 93·8% to 56·7% respectively (Table 2).

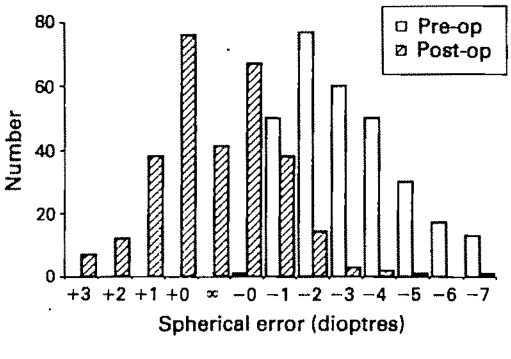

Figure 4 Spherical equivalent before and after surgery – all patients.

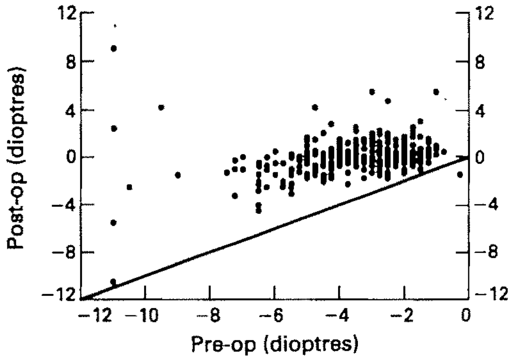

Figure 5 Spherical equivalent before and after surgery – individual patients.

In order to look at stability of refraction following surgery the spherical equivalent at the refraction nearest to 3 months after surgery was compared with that at the final follow-up visit which was at a mean of 19 months and was always greater than 12 months (Fig 8). This shows that 90% of eyes change by 1 dioptre or less over this time period and most less than 0·5 dioptre.

The need for a spectacle correction for distance vision, at final follow-up, was assessed. Sixty five per cent were not wearing any correction, 30% were wearing spectacles (although often only to drive) and 5% were wearing contact lenses.

Recorded postoperative symptoms were also analysed. The most common complaint at discharge was of diurnal variation in vision in 57 eyes. The other principal complaint was of glare or 'starburst' effect in 13 eyes which was principally experienced when driving at night. However in none of these patients were symptoms sufficiently bothersome to prevent them having surgery on their second eye.

Discussion

Radial keratotomy has been performed at Moorfields since 1981 and more than 600 procedures have been performed by one surgical team. In this series we have reviewed the results from 300 consecutive procedures performed between 1985 and 1990.

The complication rate was low with no sight threatening complications and no patient lost a line of preoperative corrected Snellen acuity as a result of surgery.

A large percentage of patients underwent

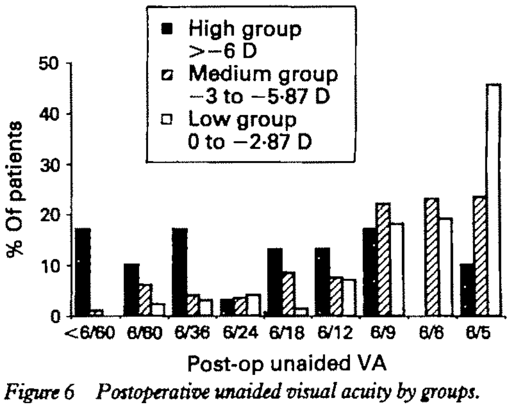

Figure 6 Postoperative unaided visual acuity by groups.

Table 1 Postoperative unaided visual acuity by groups

	Low	*Mod*	*High*
% within 1 D of emmetropia	73·8	56·5	30·0
% within 2 D of emmetropia	93·8	86·5	56·7

Table 2 Postoperative spherical equivalent by groups

	Low	*Mod*	*High*
% achieving 6/12 or better	89·2	76·5	40·0
% achieving 6/6 or better	64·6	46·5	10·0

surgery to meet the unaided visual requirements of a variety of occupations such as the armed forces, fire service, or prison service. Another large group were having difficulties with their contact lenses and most of the remainder wished to have surgery for cosmetic reasons (Fig 2).

In this series 80% saw 6/12 or better unaided postoperatively and 52% saw 6/6 or better (Fig 3). This compares with other series such as the 3 year results from the PERK trial where 76% achieved 6/12 and 52%, 6/6.[3] Postoperatively 61% were within 1 dioptre of emmetropia and 86·7% were within 2 dioptres of emmetropia. This compares with the 3 year figures from the PERK series of 58% and 81%.[3]

Thus the group as a whole achieved good results both in terms of unaided visual acuity and spherical equivalent. However, as with all refractive surgery there is variation in the effect, and the results of individual patients rather than the group as a whole (Fig 5) show that this particularly affects those patients with high levels of myopia, although there was one low myope who did not respond to surgery. It is important to note that it is not simply a question of less reduction in myopia at the higher levels of attempted correction, but much greater unpredictability shown by those eyes from this group which became significantly hypermetropic. This finding has also been described in other studies.[4,5]

In order to attempt to confirm this trend of declining predictability of surgery with increasing preoperative myopia, patients were divided into three groups on the basis of degree of myopia. Results were examined from low, moderate, and high myopes with 0 to −2·87, −3·0 to −5·87, and −6·00 dioptres or more respectively (Figs 6 and 7 and Tables 1 and 2). Both the unaided visual acuities and refractive results clearly demonstrate that the most accurate correction occurred in the low myopia group with 89% achieving 6/12 vision or better and 94% within 2 dioptres of emmetropia. The results for the group of moderate myopes may also be considered satisfactory since 76% achieved 6/12 or better and 86% were within 2 dioptres of emmetropia. However the results from the high myopia group were disappointing with only 40% achieving 6/12 or better and 57% within 2 dioptres of emmetropia. Other series have reported similar findings.[3,4]

If myopia remains significantly undercorrected after surgery the question arises of when further surgery should be undertaken. Recent studies have drawn attention to the possibility of a late hypermetropic shift in some patients after radial keratotomy.[6,7] Our results showed only small changes in refraction between 3 months after surgery and final follow up (Fig 8), at a mean of 19 months (range 12–60 months). Although this does not exclude a very late diminution in the effect of surgery it would seem reasonable to embark upon further surgery for undercorrection of myopia at 3 months after the initial procedure.

For patients, perhaps one of the most important considerations in the decision as to whether to undergo surgical treatment of myopia, is the likelihood of being able to perform most daily tasks without optical correction. In this series two thirds wore no distance correction at final follow-up, and many others used spectacles only when driving.

The retrospective nature of this study does not allow a comprehensive account of patients' symptoms. Minor visual complaints appeared to be common, especially of diurnal variation in unaided vision and glare when driving at night, but none sufficiently severe to dissuade patients from surgery on their other eye. The only patients who decided not to proceed with surgery on the second eye did so because of a poor refractive result in the first eye.

Radial keratotomy offers fairly accurate correction of myopia of between 2 and 6 dioptres. Outside this range results become unpredictable. Side effects such as diurnal variation in refraction and glare were common but generally well tolerated, perhaps because patients had been carefully counselled prior to surgery about the likelihood of such effects.

Severe complications were rare in this series, but those reported elsewhere include endophthalmitis,[8] delayed microbial keratitis,[9,10] and increased susceptibility to traumatic rupture of the globe.[11]

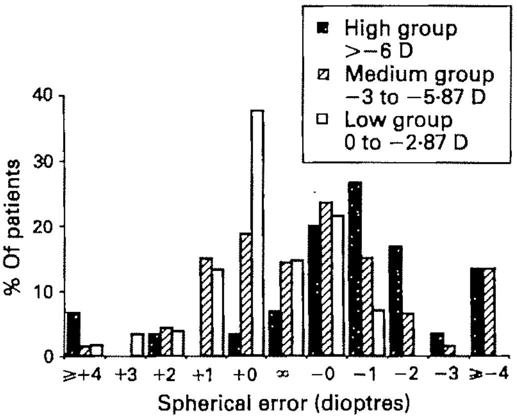

Figure 7 Postoperative spherical equivalent by groups.

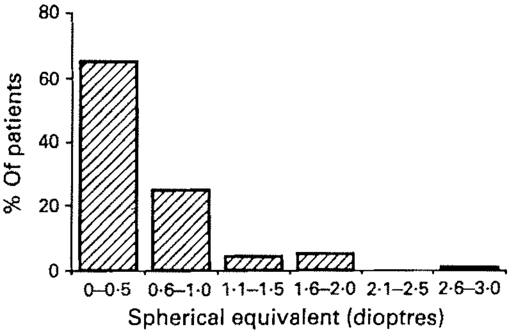

Figure 8 Change in refraction from 3 months to final visit.

It is hoped that excimer laser photorefractive keratectomy will improve the predictability of correction of myopia and reduce concerns regarding potentially serious complications. The results from radial keratotomy will at least allow an objective comparison for this new technique.

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Life expectancy in keratoconus

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Abstract

It is observed that few patients over the age of 60 regularly attend the keratoconus clinic at Moorfields Eye Hospital. The hypothesis that patients with keratoconus have a shorter life expectancy owing to underlying connective tissue related disease was tested. From patient records a sample of 337 keratoconus patients aged at least 40 years by 1991 were identified, of which 279 were living, 13 were deceased, and 45 were untraceable. The mortality rate for keratoconus patients was compared with that of the general population using actuarial English life tables. Results show no significant difference between the general population mortality rate and that of the keratoconus sample even with adjustment for social class. Possible explanations for the non-attendance of older patients are discussed.

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The keratoconus clinic at Moorfields Eye Hospital now has more than 2000 registered patients and it is observed that most patients seen are aged under 40 years and that very few patients over 60 years are seen regularly.

There are several reports linking keratoconus and connective tissue disorders such as Ehlers-Danlos syndrome, osteogenesis imperfecta,[1] and mitral valve prolapse.[2] Could it be that patients with keratoconus have a shorter life expectancy owing to underlying connective tissue related disease or is there an alternative explanation? The purpose of the present study was to investigate this matter.

Patient sample and method

The keratoconus clinic at Moorfields Eye Hospital was established in 1972 and from patient records we were able to identify a sample of 862 new patients with keratoconus who presented between June 1972 and December 1982. Of these 71 had no recorded date of birth and were excluded from the sample. From the remaining 791 those born prior to 1951 were identified as they would now be at least 40 years of age. This sample consisted of 337 patients and, of these, 112 were still attending the clinic leaving 225 unaccounted for. We attempted to trace these patients in order to determine why they were no longer attending the clinic. Those that we were unable to contact using patient records were identified through the Office of Population Censuses and Surveys as being dead or alive. Where possible the cause of death was determined. By these methods we were able to obtain conclusive data on 178 of the 225 patients no longer attending the clinic. The remainder (47) were classified as untraceable and included those patients who were known to have moved abroad. However had they died in the United Kingdom they would have been traceable.

Results

Of the study sample of 337 keratoconus patients aged at least 40 years by 1991, 279 were living, 13 were deceased, and 45 were untraceable. The sample comprised 184 males (mean age 57·75 years, range 41–79) and 153 females (mean age 51·83 years, range 41–83). The ratio of males to females was 1·20:1·00; 23·4% of the sample were aged over 50 years.

In order to assess whether the mortality for keratoconus patients was greater than that of the general population actuarial English life tables were used. These tables are used to assess general population mortality rates and the table used (ECT14) is based on the mortality experience of England and Wales during the period 1980–82 – that is, the year in which the sample was complete. From it we were able to calculate the predicted general population mortality rate by 1991 and compare it with that of the keratoconus sample. Male and females were assessed separately as their mortality rates differ (Tables 1 and 2).

There was no significant difference between the general population mortality rate and that of the keratoconus sample [χ^2=1·59 (males), χ^2=1·31 (females)].

It is known that male mortality in Great Britain differs according to social class.[3] It has been shown that the social class distribution of patients attending the keratoconus clinic at Moorfields Eye Hospital is not typical of the general population.[4] In view of these findings the figures were recalculated for social classes I and II, as these groups constituted 77% of the patients attending the clinic. The figures for the

Table 1 Females

Year of birth	*Number 1982*	*Predicted 1991*	*Actual 1991*
50	12	11·9	11
49	12	11·89	12
48	6	5·94	5
47	7	6·92	7
46	5	4·94	5
45	2	1·97	2
44	8	7·88	8
43	5	4·91	5
42	7	6·87	7
41	3	2·93	3
40	2	1·95	2
39/8	6	5·84	6
37	5	4·84	5
36	3	2·89	3
35/4	2	1·92	2
33	2	2·86	2
1903/1913 (1908)	4	2·31	1
1914/1932 (1923)	9	7·98	9
Total	110	96·74	104

χ^2=1·31; not significant

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social class adjusted males are given in Table 3. Again, no significant difference was found between the general population mortality rate and that of the keratoconus sample ($\chi^2=0{\cdot}53$). Figures for female mortality based on social class are not available.

Data on the deceased patients obtained from death certification or the patients' general practitioners are summarised in Table 4.

Table 2 Males

Year of birth	*Number 1982*	*Predicted 1991*	*Actual 1991*
50	21	20·7	21
49	30	29·6	30
48	20	19·72	20
47	16	15·75	16
46	17	16·66	17
45	10	9·8	10
44	9	8·80	9
43	6	5·85	6
42	12	11·66	12
41	4	3·86	4
40	3	2·89	2
39	5	4·8	5
38	3	2·88	2
37	3	2·88	3
36	5	4·74	5
35	4	3·77	4
34	2	1·85	2
33	3	2·76	2
1932/1920 (1926)	15	12·6	13
1913/1910	2	1	2
Total	190	181·89	185

$\chi^2=1{\cdot}59$; not significant

Table 3 Males (adjusted for social class after Haberman and Bloomfield[3])

Year of birth	*Number 1982*	*Predicted 1991*	*Actual 1991*
50	21	20·81	21
49	30	29·71	30
48	20	19·79	20
47	16	15·82	16
46	17	16·77	17
45	10	9·85	10
44	9	8·86	9
43	6	5·89	6
42	12	11·76	12
41	4	3·91	4
40	3	2·92	2
39	5	4·85	5
38	3	2·90	2
37	3	2·88	3
36	5	4·78	5
35	4	3·80	4
34	2	1·89	2
33	3	2·81	2
1932/1920 (1926)	15	12·96	13
1913/1910 (1912)	2	1·04	2
Total	190	184	185

$\chi^2=0{\cdot}53$; not significant

Table 4

Males

Year of birth	*Age at death*	*Cause*
1949	36	Accident (flying)
1938	47	Status asthmaticus
1934	46	Asphyxia; food in larynx (mentally retarded)
1940	45	Respiratory failure. Pulmonary sarcoid
1925	63	Ca larynx with 2°
1920	66	Ca bladder
1933	57	Ca oesophagus
Females		
1905	78	Carcinomatosis
1903	70	Pulmonary embolism following RTA
1950	24	Suicide: acute barbiturate poisoning
1907	82	Ca bronchus: bronchopneumonia
1948	?	?
1933	?	Myocardial infarction

Ca=cancer.

Discussion

Our results show that both male and female keratoconus patients do not have a shorter life expectancy than the general population. With regard to the male patients, even after the data were adjusted to allow for social class differences, there was still no significant difference. Thus our hypothesis that underlying connective tissue disorder shortens the life of keratoconic patients is not supported. However it must be remembered that patients with multi-system disease such as Down's syndrome may not be referred to Moorfields in view of their low success rate in contact lens wear.

The observation that most of the patients attending our keratoconus clinic are aged 40 years or less may be explained by other factors, including:

(1) older patients no longer attend because they are satisfied with their spectacle or contact lens correct vision, and do not consider that they require medical surveillance of their ocular condition;

(2) it is known that for a given patient the natural history of the disease is independent between the two eyes.[5] Thus the disease may have progressed very little if at all in the better eye and the older patients may be content with, or are resigned to, somewhat subnormal vision and no longer wear their spectacles or contact lenses;

(3) older patients who live out of London are seen by ophthalmologists or optometrists near their homes, being no longer willing to travel to London.

We plan to extend this study into future years as, though we have detected no indication of reduced life expectancy, the sample remains fairly young, less than a quarter of the patients being aged over 50 years.

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Photodamage of the conjunctiva in patients with porphyria cutanea tarda

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Abstract

Ninety two patients with porphyria cutanea tarda (PCT) were examined ophthalmically in a paired case control study. The incidence of pinguecula and of pterygium was 8 and 2 times higher respectively, in PCT patients than in the control group. The photodamage to the conjunctiva is considered to be a result of the photoactivity of uroporphyrin in the tissues.

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Porphyria cutanea tarda (PCT) is a chronic polyaetiological disorder in porphyrin biosynthesis, caused by a deficiency of uroporphyrinogen III decarboxylase in the liver cells, with typical skin and liver findings, as well as pronounced uroporphyrin excretion in the urine.[1] The skin manifestations are bullous erosive lesions triggered on the face and the backs of the hands by minor mechanical trauma, milia formation, melanosis, hypertrichosis in the eyebrows and the zygomatic area, chronic actinic skin changes, and pseudoscleroderma. The evidence suggests that the photoactivity of excess porphyrin in the plasma and/or tissues is involved in the cutaneous manifestations.

In the past few years, 92 patients with PCT have been examined ophthalmically. In this study the results of examinations of external ocular structures (lids, conjunctiva, corneas, and scleras) are reported.

Patients and methods

A paired case control study was performed.[2] For every patient with PCT, two controls were matched according to age (plus or minus 3 years was allowed) sex, and skin type on the basis of the tendency to burn and to tan[3]; furthermore, the members of the two groups worked in similar circumstances (indoor or outdoor). The frequencies of the pathological findings were compared by the χ^2 test.

PATIENTS

The study involved 92 patients with PCT (81 men and 11 women; mean age 47·3 (SD 4·8) years). The diagnosis was based on the porphyrin profiles (uroporphyrinuria and 7-carboxylporphyrinuria) and on the clinical manifestations.

CONTROL GROUP

The members of the control group suffered from psoriasis vulgaris, chronic venous insufficiency of the legs, eczema, urticaria, or allergic contact dermatitis.

Table 1 Clinical findings on external ocular structures in patients with porphyria cutanea tarda (PCT) and in a matched control group

Symptoms	*Patients with PCT (n=92)*	*Control group (n=184)*	
Hypertrichosis in the periorbital area	76	4	p<0·001
Solar elastosis in the temporal region	81	47	p<0·001
Favre-Racouchet disease	7	1	p<0·01
Erosive lesions on lids	9	0	p<0·001
Pinguecula	63	16	p<0·001
Pterygium	8	7	p>0·10

OPHTHALMIC EXAMINATIONS

Slit-lamp examination, ophthalmoscopy, visual field examination, tonometry, Schirmer test, corneal staining, and colour vision test were carried out in all patients and controls.

PORPHYRIN DETERMINATION

Urinary and faecal porphyrins were analysed by thin-layer chromatography.[4]

HISTOLOGY

The biopsy specimens were obtained from the involved conjunctiva of six patients with PCT. The tissues were fixed in formaldehyde solution (10% neutral formalin), embedded in paraffin, and sectioned in $5\ \mu m$ thicknesses. The sections were stained with haematoxylin and eosin and resorcin and fuchsin.

Results

The incidence of clinical symptoms on the external ocular structures is given in Table 1.

In 68 male and eight female patients with PCT hypertrichosis was seen in the periorbital area. Frequently, diffuse solar elastosis in the temporal region and sometimes also solar elastosis with

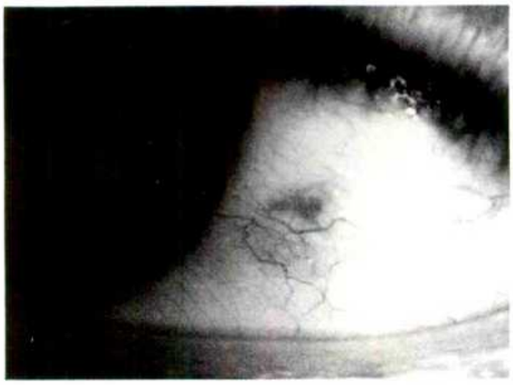

Figure 1 A nodule (yellow-brown in colour) on the temporal side of the cornea in the intrapalpebral portion of the bulbar conjunctiva.

cysts and comedones (Favre-Racouchot) were observed. These findings were significantly rarer in the control group.

In 63 patients, yellow-brown nodules were seen on either side of the cornea in the area of the lid fissure, which never extended onto the limbus (Fig 1). During slit-lamp examination we observed foamy-like degenerative changes on the surface of these nodules, which macroscopically resembled the structure of a pinguecula. Histologically, the epithelium was slightly thickened and hyperpigmentation was seen in the basal layer. The immediate subepithelial stroma contained amorphous, faintly basophilic staining material, and the stromal fibres were fragmented and partially coiled. The histological findings corresponded to the microscopic structure of pinguecula. In the control group typical pinguecula was observed in only 16 persons. Pterygium was seen in eight patients with PCT and in seven controls.

Ectropion, blepharochalasis, symblepharon, corneal and scleral abnormalities were not found in either the porphyric or the control group.

Discussion

The porphyrias are a group of diseases in which there are deficiencies of the metabolic pathway leading to the synthesis of haem. The error is recognised as lying either in the imperfect synthesis of enzymes having an aberrant structure or in the slowed synthesis of a perfect compound. The most important feature of the current classification of porphyrias is that the metabolic disorder can in all cases be localised to one specific enzyme within the haem biosynthetic pathway.

PCT is the most common form of porphyria. The basic biochemical defect is a reduced activity of uroporphyrinogen decarboxylase in the liver, which results in the overproduction and increased excretion of uroporphyrin and polycarboxylated porphyrins. The cause of the reduced enzyme activity is unclear, but appears to be a result of complex interactions of both genetic and acquired factors.[1]

In the present study, actinic damage of the periorbital skin was observed in 88 of the 92 PCT patients, with erosive lesions on the lids in nine. Pinguecula and pterygium were eight and two times, respectively, more frequent in the PCT group than in the matched controls (Table 1). Though other authors have described lid scars and ectropion,[5 6] we did not observe these in any of the patients, nor did we see those severe changes of the externed ocular structures (scleral ulceration and perforation, and symblepharon) observed in congenital porphyria.[7-9]

Sunlight-induced skin lesions are clinically characteristic of PCT. The evidence suggests that the phototoxic effect of porphyrins is involved in the cutaneous manifestations. The absorption of light with a wavelength of around 400 nm (which corresponds to the peak in the absorption spectrum of the porphyrins), and the more penetrating light of the subsidiary peaks between 500 and 600 nm, raises the porphyrin to its singlet or triplet excited state. Excited porphyrins can react directly with tissues and molecules within the cell, or they allow transfer of the excitation energy to molecular oxygen, thereby producing oxygen radicals and peroxides.[10] The exposure of porphyrins to 400–410 nm radiation results in complement activation[11] and the release of mediators from mast cells.[12] The biological effects of oxygen radicals, mast cell-derived mediators, and anaphylotoxin, generated as a consequence of complement activation, may account for the damage of the sunlight-exposed tissues.[13] Though the photoactivity of the porphyrins explains many aspects of the pathophysiology of tissue damage in porphyria, there are still many unanswered questions. For example, what accounts for hypertrichosis in the periorbital areas of patients with PCT?

Pterygium and pinguecula are consequences of the actinic damage of the conjunctiva.[14] This is indicated by the facts that they appear in every case in the interpalpebral fissure, their frequency increases in proportion to age, the time spent in sunlight and the intensity of the solar radiation, and their tissue structures are highly reminiscent of that of solar elastosis of the skin. We consider that their high incidence in PCT is a consequence of the phototoxic effect of the uroporphyrin accumulated in the tissues. We did not observe the previously reported serious effects of photodamage in porphyria – that is, ectropion, symblepheron, blepharochalasis, and scleromalacia. The explanation of this may be that a longer time is required for their emergence, but in our cases the treatment (phlebotomy and chloroquine) led to normalisation of the porphyrin excretion in 3–6 months.

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Foveal photopigment kinetics – abnormality: an early sign in myotonic dystrophy?

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Abstract

Twelve subjects with minimal expression of the myotonic dystrophy (MyD) gene were investigated by retinal densitometry, a technique which has been used to study the properties of photopigments in the living eye and to detect photoreceptor abnormalities. Other investigations included slit-lamp examination, funduscopy, raleigh matches with the anomaloscope, tonometry, and neurological examination, including electroretinography (ERG) and pattern visual evoked potentials recording. Foveal densitometry demonstrated reduced values of the macular photopigment density difference with normal photopigment kinetics in early phases of the disease, even in asymptomatic individuals. The densitometric values correlated with decreased amplitudes of the photopic ERG a-wave. These findings may be explained by loss or dysfunction of the outer segments of foveal receptors. It is yet unknown whether or not these changes are secondary to other observed neuroretinal abnormalities in MyD. The most likely explanation might be an abnormality of the Na, Ca:K exchanger at the level of the outer segments of the photoreceptors whether or not in combination with a dysfunction of voltage generation systems, involving both photoreceptors and retinal pigment epithelium.

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Myotonic dystrophy (MyD) or Curschmann-Steinert disease is an autosomal dominant multisystem disorder of which the gene abnormality is localised on chromosome 19.[1,2] DNA diagnosis of MyD is possible with both sensitivity and specificity higher than 96%.[2] It shows variable gene penetrance and expressivity, and the onset of MyD varies from early infancy to old age.[3] An alteration in the intrinsic biochemical composition of the cell membrane, affecting the entire body, has been proposed as the pathogenesis of MyD.[1]

Ocular abnormalities associated with MyD are cataract, hypotonia, and chorioretinal changes. Several authors reported the considerable electroretinal alterations in MyD patients, even before fundal changes and other expression of the abnormal gene.[1,4-14] A common finding was the reduction of the b-wave amplitude in the electroretinogram (ERG) both in scotopic and photopic conditions.[4-12] Visual evoked potential (VEP) recording in MyD repeatedly showed prolongation of latency or decrease of amplitude.[12] Recordings of the pattern ERG (PERG) and pattern VEP (pVEP) simultaneously demonstrated abnormalities that occurred independently of one another. The authors also found subnormal electro-oculogram Arden indices. They suggested that the pathological process may affect both the retina and post-retinal intrinsic visual pathways.

Both clinical[4,5] and histopathological[15-21] evidence of photoreceptor and other neuroretinal abnormalities has been reported in progressive stages of MyD. The purpose of this study was to investigate the early expression of retinal abnormalities in MyD, including those of foveal photoreceptors. We have used retinal densitometry to examine the macular photoreceptors of eyes of a group of minimally affected MyD patients. To our knowledge this technique has never been utilised in MyD.

Material and methods

SUBJECTS

Twelve patients, eight females and four males, were examined. Informed consent was given by all patients. They all either had a positive family history for MyD and myotonia, or a clinical diagnosis of MyD, confirmed by DNA investigation (Laboratory of Clinical Genetics, Radboud Hospital, Nijmegen, the Netherlands). All patients were submitted to neurological and ophthalmic examination, including testing of visual acuity, funduscopy, slit-lamp examination, and tonometry (Goldmann applanation tonometer). Inclusion criteria for the study were a visual acuity of at least 0·8 after correction and no or minimal lens abnormalities (sporadic polychromatic crystals or white dots) and a Karnofsky index exceeding 80. An age matched group of 12 healthy subjects was used as control.

INVESTIGATIONS

Densitometry

The density of foveal cone pigments was measured with the Utrecht densitometer which has been described in detail by van Norren and van der Kraats.[22]

Briefly, the light reflection at the fundus is determined at a range of wave lengths through the visual spectrum. The light needed for this measurement is so dim that influence on the visual pigments is minimal. The spot of light (30 W halogen lamp) at the fundus is restricted to 2·8 degrees in this measurement. Reflections of the fundal lights are collected by a photomultiplier in photon-counting mode and processed by a computer. Bleaching is possible with a separate light path which provides a retinal illumination of 5·6 log Td. The change in reflection from the retina of a healthy person before and after bleaching determines the 'two-way density'. The pupils of all subjects were dilated with tropicamide. A bar made of dental impression compound, and two temple pads were used for immobilisation of the head. The fundus camera was adjusted to obtain the highest possible reflection as measured by the photomultiplier. Subjects fixated cross-hairs centred with the stimulus field. The fovea was bleached for 2 minutes. After switching off the bleaching light the regeneration of cone pigment was followed until the density trace had reached a stable level. Then the bleaching light was switched on again for 2 minutes. The density trace should then return to the fully bleached condition, permitting the reliability of the measurements to be checked. The changes in retinal transmittance between fully dark adapted and fully bleached states of the retina are related to the photopigment density of the test area.

Basically, two values can be extracted from the data: the density difference and the time constant of pigment regeneration. The density difference is the change in the logarithm of the measuring light reflectance to the reference light reflectance, from fully bleached to fully adapted states. The time constant of pigment regeneration can be estimated from the initial 180 seconds of adaptation following extinction of the bleaching light. In this study we only present the data obtained at 554 nm, being the peak of the absorption spectrum. Peripheral measurements, investigating the rods take considerably longer, since the adopser regenerates slow. In our subjects occasionally denture fitting problems and lack of concentration – common signs of MyD – interfered with the measurements.

VEP and ERG

Pattern visual evoked potentials and ERG measurements were made with a laboratory built system for clinical electrophysiology of vision.[23] The ERG was obtained in both scotopic and photopic conditions, using corneal electrodes and three different white light stimulus intensities. VEP recording was done under standard conditions, using 11′, 46′, and 92′ settings in the black-and-white chequerboard reversal pattern.

Anomaloscope

Colour matching was investigated with a Nagel type I anomaloscope by a standard technique.[24]

Results

The ages of the patients ranged from 12 to 39 years (mean 26 years) and the general disability rated by Karnofsky index[25] varied from 80 to 100 (mean 90). The duration of clinical disease varied from 0 to 408 months (mean 71 months).

A summary of the main ophthalmic results is displayed in Table I. Slit-lamp examination revealed minimal lens opacities in four patients (30%) and characteristic polychromatic crystals in three patients (25%), while in five patients (42%) no abnormalities were detected. Funduscopy did not show morphological changes of the retina in any of the patients. The visual acuity varied from 1·2 to 0·8 (mean 0·9). Anomaloscopy showed no protan or deutan defects.

Seven of nine patients had low intraocular pressures bilaterally, while two patients had low normal pressures (mean 12·7±2·3; normal values 15·5±2·5).[26]

In four out of 23 eyes (17%) the scotopic ERG showed a significant decrease of the a-wave amplitude and in only 1/23 eyes (4%) a significant decrease of the b-wave. An increase in implicit time was noticed in 10/23 eyes (43%) for the scotopic a-wave and 3/23 (12%) for the scotopic b-wave. In photopic conditions 8/23 eyes (35%) showed a decrease of the a-wave amplitude and in 7/23 eyes (30%) a decrease of the b-wave amplitude. An increase in implicit time was recorded in 2/23 (8%) eyes for the photopic a-wave and in 4/23 (16%) for the photopic b-wave.

Pattern VEP recording with 11′ pattern reversal blocks showed a significant prolongation of the P100-latency in four patients (30%). In five eyes (42%) a decrease of the VEP amplitude was noted. No significant hemispheric asymmetry was seen. In two eyes (16%) both VEP amplitude and latency were abnormal. Only five eyes (42%) had normal VEP data. There was no clear correlation between VEP and ERG data.

In six patients (50%) foveal densitometric measurements showed a significant decrease of

Table I Ophthalmic findings in myotonic dystrophy

							Scot ERG				*Phot ERG*			
		Vision			*Densito*		*Amplitude*		*Latitude*		*Amplitude*		*Latitude*	
Patient	*Duration (months)*	*Right*	*Left*		*Right*	*Left*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
AB[a]	12	1·0	1·0	cp	–	0·21	–	N	–	N	L	L	N	H
AB	24	1·0	0·8	vac.	0·22	0·18	N	N	N	N	L	L	N	N
GF[a]	60	1·0	1·0	pcc	0·25	–	N	N	N	N	–	–	–	–
EG	144	0·8	1·0	dots	0·35	0·37	N	N	H	N	N	N	N	N
JM[a]	0	1·2	1·2	dot	0·21	–	–	H	–	N	L	N	N	H
JM	0	0·9	0·9	N	0·33	0·35	N	N	N	N	N	N	N	N
JS	408	1·0	0·6	dcp	0·37	0·40	N	N	H	N	N	N	N	N
JS	118	1·0	1·0	cp	–	0·23	N	N	N	H	N	N	H	N
JS	72	1·0	1·0	dcp	0·36	–	L/N	N	H	N	N	N	N	N
JV	19	1·0	–	dot	0·18	–	L/N	L/N	N	H/N	L/N	L/N	N	N
MV	0	1·0	1·0	dots	0·12	–	N	N	H	N	L/N	L	N	N
GY	0	0·9	0·9	N	0·39	0·43	L	N	H	N	N	N	N	N

N, normal; L, decreased; H, prolonged or increased; –, no result; pcc, polychromatic crystals; cp, crystals in lens cortex posterior; dots, dots in lens cortex posterior; dcp, dot(s) and crystals in lens cortex posterior; densito, foveal two-way densities – normal: age matched: 0·38 (SD 0·12).

[a] Values of peripheral densitometry
patient 1: 0·20 (N)
patient 3: 0·13 (abnormal)
patient 5: 0·17 (N)

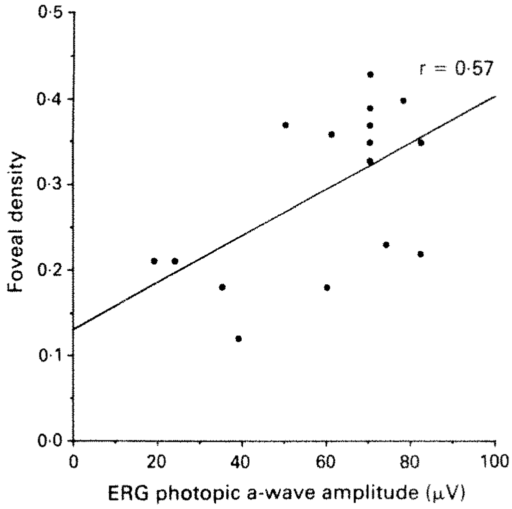

Figure 1 The amplitudes of a-wave of the photopic ERG are plotted against the values of foveal densitometry. The best fitting line has an r value of 0·57 (Spearman's rank correlation) and p=0·02 (Wilcoxon rank sum test) to reject the nul option.

the two-way density. The mean density of all patients tested (0·29 (SD 0·09)) was significantly lower than the mean of the age-matched control group (0·38 (SD 0·12)). The time constants of pigment regeneration of the patients (mean 66 (SD 6) seconds) were in the normal range (mean 69 (SD 8) seconds).

Both peripheral retinal densitometry and ERG in patients 1 and 5 showed no abnormalities, but foveal densitometry was significantly abnormal in both cases. In patient 3 the peripheral densitometric measurement was low, 0·13 (normal 0·18 (SD 0·04)) (Table I).

The Arden index of the EOG was subnormal in 6/12 eyes (mean 181% (SD 15·7), range 161–193).

Myotonia was noted in seven patients (58%). Ptosis was absent in six patients (50%), minimal in one (8%), moderate in three patients (25%), and severe in the remaining two patients (16%). Weakness of the limb muscles was found in three patients (25%), varying from minimal to moderate.

Discussion

Foveal densitometry demonstrated subclinical abnormalities of foveal photoreceptors in 50% of our patients with minimal (early) expression of the MyD gene (Table I). Even in a 12-year-old asymptomatic DNA positive individual (patient 11) a strikingly abnormal value was noticed.

The reduced two-way density may be caused by loss or dysfunction of photoreceptors or by a reduced effective optical density of foveal cones due to shortened outer segments. Other causes include active or chronic serous leakage of subretinal fluid with photoreceptor disorientation and abnormally high stray light levels secondary to lenticular opacities. The latter is unlikely because lens opacities in our patients were negligible. Serous leakage of subretinal fluid can be excluded by normal funduscopy findings. The results of the normal pigment regeneration times excludes serous leakage because this phenomenon is usually associated with increased pigment regeneration times.[27] Normal findings with the Nagel anomaloscope, which would be most sensitive to cone pigment density changes occurring in individual cones, such as shortened outer segments,[28] make such alterations less probable. Therefore, we argue in favour of loss or dysfunction of photoreceptors to explain the reduced densitometric values.

Additionally, the peripheral retina of three cases was examined using retinal densitometry. Whilst in all three patients the foveal densitometry findings were abnormal, in two out of three the peripheral two-way densities were normal.

Though the number of investigated eyes is limited, these findings may indicate predominant involvement of the macular area in early stages of MyD. The predictive power for densitometry for family members of patients with MyD is very high (odds ratio: 6, 95% CI, 0·728–277 CIA statistics) compared with the total of all performed ophthalmic tests (odds ratio: 10, 95% CI 1·42–442).

In contrast with previous authors (see Introduction), who reported reduced amplitudes of the scotopic b-wave as the most frequent ERG abnormality, our study showed a significant predominance of *photopic* ERG a and b-wave abnormalities. The latter is not due to a sample error. Compared with the study of Pinto *et al*[12] a difference of proportions is significantly different (difference of confidence interval: 0·560, 99% CI 0·151–2·58, CIA statistics).

Furthermore, the photopic ERG a-wave amplitude showed a significant (Wilcoxon test, p=0·02) correlation with the foveal densitometric values. The decrease of amplitude of 11′ pVEP shows a trend for correlation with foveal densitometric findings (Wilcoxon test, 0·05< p<0·10). These findings also point at subclinical (macular) cone changes in early onset of MyD.

Only in a minority of this selected patient group, a decrease of the b-wave of the scotopic ERG could be detected (Table I). Presumably, the scotopic b-wave abnormality seems a late manifestation.[21]

Several authors described a decrease of the scotopic b-wave,[29 30] which may be associated with a disturbance in retinal Mueller cells. Another report[12] suggested involvement of ganglion cells. Retinal pigment epithelial (RPE) changes have been clinically[4 5 31] and histologically observed.[15-18] Whether the photoreceptor and other neuroretinal (Mueller and ganglion cells) alterations are primary or secondary to changes in the RPE, remains a matter for discussion. Sarks *et al*[21] argue in favour of the principal pathological changes to occur at the level of the RPE, based on the minimal fallout of photoreceptors, despite relatively good vision and slightly affected electrophysiological tests; while, in those cases the RPE was grossly irregular and hypertrophic, with distorted villi, containing – in particular under the fovea – large amounts of (melano) lipofuscin.[21] If the EOG is abnormal, a much larger area than the foveal (receptors) must be affected (see above). It is intriguing to speculate that in MyD some as yet unknown metabolic disturbance of the RPE cells may result in dysfunction and subsequent variable atrophy of photoreceptors.

Where does this leave us with the retinal pathophysiology? The difficulty could lie in the voltage generating mechanisms of the slow oscillations at the basal membrane, the concentration of the 'light peak substance (lps)' at the level of the photoreceptors or the transmittance of the message across the apical membrane through the RPE cytoplasm to the basal membrane. Less likely hypotheses we cannot exclude are a delay or a block in the messenger system or a defective voltage generation system of RPE and photoreceptors, similar to the one demonstrated in the muscle and erythrocyte membranes. Nevertheless, the 'lps' concentration change abnormality at the level of the photoreceptors[32] might explain both ERG, EOG, and densitometry findings. Therefore, we postulate an abnormality in a Na, Ca:K dependent exchanger in the outer segments to be the primary defect, taking into account knowledge of membrane pathophysiology. The mRNA of the MyD gene encodes a protein kinase polypeptide, which is known to modulate the activity of excitable cells by phosphorylation of ion channels.[33,34] The (muscle) membrane has a decreased resting potential, with a value close to the threshold for activation of Na^+ channels and the presence of specific (apamin sensitive) Ca^{2+} activated K^+ channels.[35,36] Besides, the Na^+-K^+-ATPase activity is decreased and the voltage dependent Ca^{2+} channels are active under conditions in which they are normally inactive.[37] Therefore, instead of 3 moles of Na^+ ion exchange for 2 moles of K^+ ion in control cells, a 2 Na^+ for 2 K^+ ion exchange occurred in MyD cells.[38] Altered inward sodium transport and extracellular leaking of potassium is involved in the generation of action potentials or regulation of resting potentials.[39–41] The defective regulation of ion transport could initiate or contribute to abnormal cellular functions in MyD.[41] Remarkably, in more advanced disease the Mueller glial cell becomes affected. In particular this cell, with a high resting potential, appears to be most sensitive to potassium changes at physiological levels compared with neurons.[42] We hope that future studies may obtain additional information on the locality and mechanisms of the retinal dysfunction in MyD.

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Intravenous sedation for ocular surgery under local anaesthesia

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Abstract

Anterior segment ophthalmic surgery is commonly performed under local anaesthesia. In order to improve patient comfort, a variety of sedation techniques has been employed in the past. The object of this study was, firstly, to determine whether continuous intravenous sedation during surgery offered any advantages in patients premedicated with temazepam and metoclopramide, and, secondly, to compare midazolam to propofol for this purpose. Forty nine patients were randomly allocated to receive no intravenous sedation (n=15), continuous propofol infusion (n=17), or continuous intravenous midazolam infusion (n=17) after peribulbar anaesthesia. Each technique provided cardiovascular and respiratory stability and allowed early recovery with minimal postoperative sequelae. Unexpected ocular field movement occurred more commonly in the patients receiving intravenous sedation, although statistical significance was not shown (p=0·06). Significantly more patients in the intravenous sedation groups reported amnesia (p=0·03). Patient acceptability was good irrespective of the technique used. This study suggests that continuous sedation using propofol or midazolam is not beneficial and should be avoided in ophthalmic patients who have received a simple premedication.

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Retrobulbar or peribulbar anaesthesia is widely used for anterior segment ocular surgery. Local anaesthesia is cost effective, allows a rapid recovery with early hospital discharge and is popular with patients.[1 2]

It has been suggested that patient comfort might be improved during surgery by using intravenous sedation.[3] Several techniques have been advocated in the past with varying success and a range of complications.[3-6] The ideal sedative amnesic technique should be reliable, safe, and allow early recovery with minimal postoperative sequelae.

New drugs have become available which are ideally suited to outpatient surgery. Propofol is an intravenous anaesthetic agent which has favourable pharmacokinetic properties and is in widespread use.[7 8] Midazolam, a new imidazobenzodiazepine, has distinct advantages over diazepam and has also been used for sedation during diagnostic and therapeutic procedures.[9]

Despite the excellent record of both drugs when used for intravenous sedation during other surgical procedures, to our knowledge only two trials have reported the use of midazolam and none the use of propofol, during ophthalmic surgery under local anaesthesia.[6 10] The object of this study was to compare three groups of patients, randomly divided to receive no intravenous sedation, a continuous intravenous infusion of propofol, or a continuous intravenous infusion of midazolam during surgery. All patients received a standard oral premedication 2 hours prior to commencement of surgery.

Patients and methods

Forty nine consenting patients over the age of 50 years requiring anterior segment surgery were studied. Patients with a history of alcohol or drug abuse, an allergy to the drugs to be used in the trial, or those receiving narcotic, barbiturate, or psychotropic drugs were excluded; as were patients with epilepsy, signs of congestive cardiac failure, or evidence of renal or hepatic disease. Controlled hypertensive or diabetic patients were included.

A standard premedication of 10 mg temazepam and 10 mg metoclopramide was administered by mouth 2 hours prior to the commencement of surgery in all cases. The patients were divided into three groups, using a table of random numbers. One group received no intraoperative sedation, one group received a continuous intravenous infusion of propofol, and one group received a continuous intravenous infusion of midazolam during the surgery.

A peribulbar block was performed prior to the commencement of intravenous sedation by the same surgeon in a standard fashion, using a mixture of 5 ml bupivacaine 0·5%, 5 ml lignocaine 2%, and hyaluronidase 1500 IU. The adequacy of the block was verified and additional local anaesthetic given if the block was incomplete. The surgeon was unaware of the method of sedation to be used.

All patient monitoring was conducted by the same anaesthetist (BM). The heart rate and rhythm were continuously monitored using a Hellige Servomed SMK ECG apparatus. A non-invasive blood pressure monitor (Dinamap, Critikon) was used to measure the blood pressure every 5 minutes. Oxygen saturation was monitored continuously (Oxyshuttle, Critikon), as was end-tidal carbon dioxide using a nasal cannula (Datex, Multicap). A stethoscope was strapped to the trachea in order to determine the development of airway obstruction with increasing sedation.

Airway obstruction was arbitrarily graded as follows: grade 1 – completely clear airway; grade 2 – slightly increased breath sounds; grade 3 – noisy breathing; and grade 4 – complete obstruction requiring manual adjustment of the head position to ensure an improved airway. The level of sedation, assessed during the surgery, was

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based on the patients' response to questioning and was also arbitrarily graded into four levels: level 1 implied a patient who did not appear drowsy; level 2 a patient who was drowsy but cooperative; level 3 a patient with cooperative dysarthria; and level 4 a patient who demonstrated no vocal response to questioning.

Patients receiving no sedation during the surgery had an intravenous line inserted and received an initial bolus of normal saline, followed by a continuous saline infusion. In those patients in whom propofol was used, a slow initial bolus of propofol 1% was given to achieve cooperative dysarthria (sedation level 3) and then an infusion of propofol commenced at 1·0 mg/kg/hour. Patients in the third group received a slow bolus of midazolam 0·025% to achieve the same sedation level as in the propofol group and thereafter an infusion of midazolam was commenced at a rate of 1 mg/hour. In both sedation groups, the rate of infusion was adjusted to maintain a constant level of sedation.

During the operation the anaesthetist and the surgeon independently assessed patient and operative field movement.

The infusions were stopped immediately after the completion of surgery and 5 minutes later the patient was asked prerehearsed questions (date of birth, address). The orientation of the patient was reassessed 1 hour later. The next morning, while the surgeon was still unaware of the drugs used, the patients were asked whether they had been aware of the operation and specifically whether they could remember the questions asked during the procedure. They were questioned about the presence of postoperative ocular pain, headache, nausea, their dreams of the previous night, and their subjective perception of the technique used. The intravenous site was examined.

The normally distributed data were subjected to statistical analysis using analysis of variance with the Tukey multiple range test to identify significantly different groups. Non-parametric tests were used for all other data analysis: Kruskal Wallis for comparing scores in groups of patients, and χ^2 analysis, or Fisher's exact tests for comparing distributions: $p<0{\cdot}05$ was considered statistically significant.

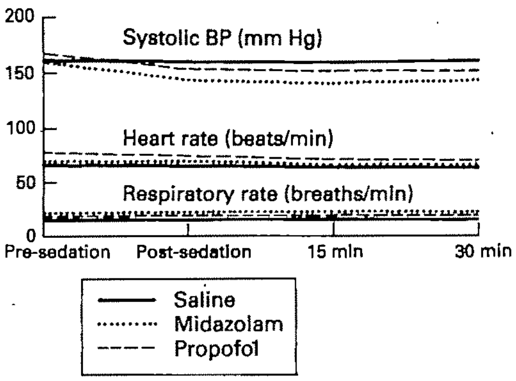

Figure 1 Cardiovascular and respiratory changes during the procedure in the three groups. There are no significant differences.

Table 1 Patient data

	Saline (*n*=15)	*Midazolam* (*n*=17)	*Propofol* (*n*=17)
Sex			
Male	9	8	7
Female	6	9	10
Race			
White	3	5	2
Mixed	8	10	13
Black	4	2	2
Age (mean in years)	69·0	64·5	66·5
Weight (kg)	70·0	67·7	70·4
Duration of operation (minutes) (SD)	38·0 (2·2)	39·6 (2·1)	39·7 (1·9)

Results

No patient was excluded from the study once the premedication had been administered. One patient required a second injection of local anaesthetic (1 ml retrobulbar lignocaine 2%) for an incomplete block, one had a small abduction movement, and one had pain with the insertion of a superior rectus bridal suture. All the others had good akinesia and local analgesia.

The three groups were statistically comparable and the mean duration of the procedures was similar in each group (Table 1). The mean total dose of midazolam was 1·41 mg (standard error 0·13) and the mean infusion rate was 1·04 mg/hour (standard error 0·03). The mean total dose of propofol was 43·2 mg (standard error 4·0) and the infusion rate was 7·7 ml per hour (standard error 0·4).

There were no significant differences between the three groups in respect of cardiovascular variables (Fig 1). Though 47% of patients (8/17) receiving intravenous propofol had a rise or a drop of systolic blood pressure of more than 20 mm Hg, compared with 29·4% (5/17) receiving midazolam and 20% (3/15) receiving saline infusion, this was not statistically significant. A pulse rate drop of more than 20 beats/minute was noted in two patients receiving intravenous propofol.

Minor airway obstruction (snoring) occurred with equal frequency in the midazolam group and the propofol group, but this was not statistically significant when compared with the saline group (Fig 2). One patient receiving propofol

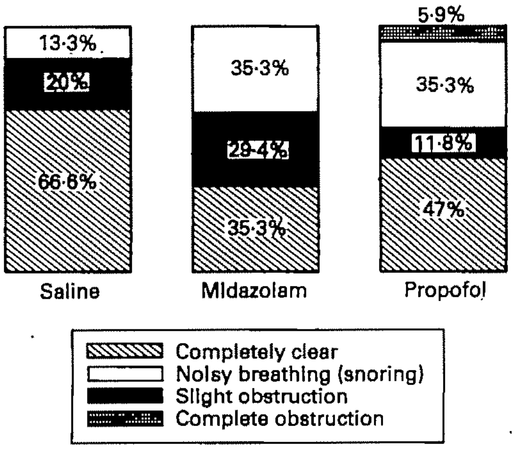

Figure 2 The incidence and severity of airway obstruction in each group. There are no significant differences. Grading: 1 – completely clear; 2 – slightly increased breath sounds; 3 – noisy breathing (snoring); 4 – complete obstruction requiring manual airway correction.

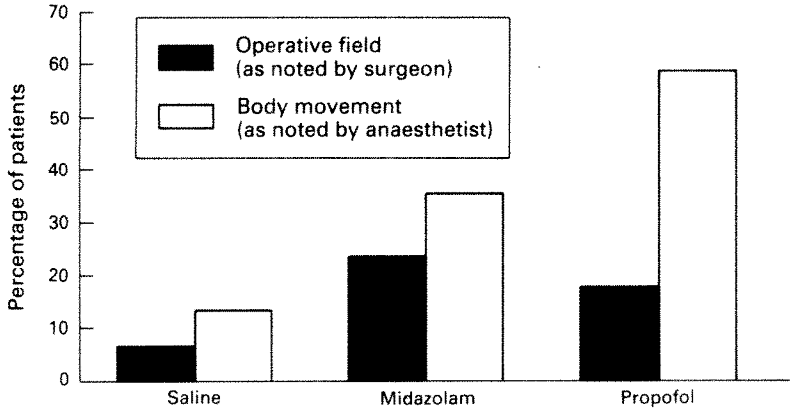

Figure 3 Incidence of movement noted by surgeon or anaesthetist. Incidence of patient movement noted by anaesthetist (fidgetting) was significantly greater in the propofol group than in the saline group.

had a complete airway obstruction which necessitated repositioning of the neck. There was no significant difference between the three groups in terms of the minimum oxygen saturation or the maximum end tidal pCO_2 and in all patients these parameters remained satisfactory throughout the surgery. In one patient in each group the minimum oxygen saturation dropped below 95%. In one patient receiving midazolam the minimum saturation was 89%, in one receiving propofol 91%, and in one receiving saline 93%. In two of these patients this was clearly related to minor airway obstruction.

The anaesthetist noted more unexpected patient movement in the propofol group and in the midazolam group than in the saline group (Fig 3). There was a significantly greater incidence of movement in the group receiving propofol compared with the saline group (p=0·009). Movement of the operative field was noted by the surgeon in one patient in the saline group who had a small abduction movement related to an inadequate block. One of four patients in the midazolam group and three patients in the propofol group had a major unexpected head movement, but in no patient was the surgery compromised (Fig 3). Statistical significance was not demonstrated when operative field movement was compared in patients receiving intravenous sedation with those not receiving intravenous sedation (p=0·06).

Five minutes after stopping the infusion each patient in all three groups was able to answer prerehearsed questions and was aware of his surroundings. All patients remained fully orientated when assessed in the recovery room 1 hour later.

There was no significant difference between the three groups in terms of postoperative pain, nausea, headaches, or dreams when assessed the following morning (Table 2). No patient recalled experiencing pain with the intravenous infusion of the previous day, but one patient who had received intravenous midazolam was found to have localized tenderness over the intravenous site. Patients receiving propofol or midazolam were less aware of the operation than patients receiving saline (p=0·03 and p=0·02 respectively) (Table 2). Fewer patients in the midazolam group (13/17) would have chosen a similar technique for another procedure, than those in the propofol group (17/17). This was statistically significant (p=0·031). When comparing those patients who had received no intravenous sedation with those who had received intravenous sedation, patients were equally satisfied irrespective of the technique used (Table 2).

Table 2 Patients' opinions of the sedation technique

	Saline (n=15)	*Midazolam (n=17)*	*Propofol (n=17)*
Operative amnesia	0 (0%)	5 (29·4%)	6 (35·3%)
Postop eye pain	1 (6·6%)	0 (0%)	1 (5·95%)
Postop headache	4 (26·6%)	6 (35·3%)	8 (47·1%)
Postop nausea	0 (0%)	0 (0%)	2 (11·8%)
Postop dreams	4 (26·65%)	2 (11·8%)	2 (11·8%)
Same technique again	14 (93·3%)	13 (76·5%)	17 (100%)
Satisfaction	15 (100%)	15 (88·2%)	17 (100%)

Discussion

Many single and multiple drug sedation regimens have been advocated for use during ophthalmic surgery under local anaesthesia. Intravenous propofol and midazolam have been successfully used for sedation during other surgical and diagnostic procedures under regional anaesthesia.[11-15] It has been our practice to use a simple oral premedication of temazepam and metoclopramide 2 hours prior to surgery. The object of this study was to examine whether there would be any advantage in using additional intravenous sedation using the new drugs, propofol, and midazolam.

The greatest potential advantage of propofol is early recovery with rapid return to normal psychomotor function.[7 8] There is a low incidence of postoperative nausea and the drug has reliable amnestic properties. For the ophthalmologist, a potential benefit during anterior segment surgery is a significant decrease in the intraocular pressure.[16] When used as a continuous sedation technique, the infusion rates need to be determined for each patient and have to be adjusted during surgery to ensure that sedation does not become too light or does not progress into full anaesthesia.[17]

Midazolam has the anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and anterograde amnestic effects characteristic of benzodiazepines.[9] The drug is effective in reducing the intraocular pressure.[10] Compared with diazepam, midazolam produces less postoperative drowsiness, more amnesia, and less venous irritation. Recovery from midazolam appears to be less rapid than recovery from propofol.[15]

As expected from the pharmacokinetic characteristics of both drugs, there was rapid reversibility of action and all patients in both intravenous sedation groups were aware of their surroundings and could correctly answer questions 5 minutes after the drugs were stopped. It was statistically significant that more patients who had received midazolam and propofol were unaware of the operation than those receiving a premedication alone.

There were no significant differences between the three groups in terms of cardiovascular stability, oxygen saturation, and expiratory levels of pCO_2. While 35·3% of patients in the midazolam group and 41·2% of patients in the propofol group had a limited degree of airway obstruction, this was not significant when compared to patients receiving no intravenous sedation. One patient receiving propofol had a complete obstruction of the airway which necessitated repositioning of the neck. These findings differ from a previous trial comparing propofol with midazolam by infusion, where 'excellent' airway maintenance was found.[15]

During ophthalmic surgery under local anaesthesia an uncontrolled and unexpected movement of the head, and consequently movement of the operative field, could result in major surgical complications. The anaesthetist noted more body movement in the propofol group and in the midazolam group than in the saline group. However, statistical significance was only demonstrated for the propofol group. In both intravenous sedation groups the surgeon noted head movement, including a major movement in one patient receiving midazolam and in three patients receiving propofol. This occurred because the patients fell asleep and awoke unaware of their surroundings or because communication was reduced. Studies comparing intravenous propofol and midazolam have reported similar problems.[14 15] Despite the excellent record of these drugs in other forms of surgery performed under local anaesthesia, this single side effect makes the technique of sedation as described in this study undesirable for ophthalmic surgery.

On assessment of the patients' wish to have a second procedure using a similar technique, there was no difference statistically between those who had received intravenous sedation and those who had received no intravenous sedation. Except for two patients who had received midazolam, patients were satisfied irrespective of the technique used.

This study suggests that continuous intravenous sedation with propofol or midazolam is not beneficial in well prepared and informed patients who have received a simple premedication of temazepam and metoclopramide. In our opinion, the ideal patient undergoing ophthalmic surgery is conscious, cooperative, and pain free. The techniques described in this report do not consistently produce these conditions and should therefore be avoided in ophthalmic patients.

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Prolongation of rat corneal graft survival by treatment with anti-CD4 monoclonal antibody

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Abstract

A rat model of orthotopic corneal graft rejection was used to investigate the effect of depletion of subpopulations of immune cells by treatment with monoclonal antibodies. Though CD4$^+$ cells were not eliminated completely by anti-CD4 monoclonal antibodies there was a profound delay in the rejection times of orthotopic corneal allografts. Furthermore a third of the CD4$^+$ depleted animals failed to reject corneal allografts by 100 days post grafting. Despite an almost complete depletion of circulating CD8$^+$ cells, the anti-CD8 antibody treated animals rejected corneal allografts in a similar time course to allografted controls treated with a non-reactive control antibody OX21. These results demonstrate that CD8$^+$ T-cells are not required for rejection of corneal allografts whereas CD4$^+$ T-cells play a critical role in the rejection response. Treatment with anti-CD4 antibodies may have a useful clinical application.

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Human corneal grafts are not rejected in the majority of recipients unlike allografts of most other organs, and this lower susceptibility to rejection is termed 'immunological privilege'.[1] However privilege is relative and corneal grafts in eyes that have suffered inflammation have a high failure rate.[2] The main cause of graft failure is immunological rejection[3] but the mechanisms of corneal graft rejection are poorly understood. It has been proposed that CD4$^+$ T-helper cells, CD8$^+$ T-cytotoxic cells, and inflammatory cells are involved in solid organ graft rejection.[4] Though recognition of foreign antigens via the afferent limb of the immune system by specific T-cells is important in mediating corneal graft failure[5] the precise effector mechanism is unknown. There is little direct evidence to support the role of cytotoxic CD8$^+$ T-cells as the effector cells of corneal graft rejection, though anti-donor splenic CD8$^+$ T-cells have been generated in vivo from corneal grafted animals.[6] However the association of a particular in vitro immune response with graft rejection does not necessarily imply that it is a requirement for rejection.[7]

It would seem from observations of the rejection of other organs that the CD4$^+$ T-cell plays a critical role in allograft rejection, whereas the CD8$^+$ T-cell does not.[8-10] Indirect evidence derived from immunohistochemical analysis of cells infiltrating rejecting corneal allografts in rats failed to identify significant infiltration by CD8$^+$ cells though a heavy infiltration of macrophages was identified.[11 12] That CD8$^+$ cells are neither necessary nor sufficient to cause corneal graft rejection in mice was recently suggested by depletion experiments in mice.[13] We studied the survival of corneal allografts in adult euthymic rats depleted of either CD8$^+$ or CD4$^+$ cells and prolonged by regular monoclonal antibody (mAb) therapy. We found that the rat corneal allograft rejection response was not affected by profound CD8$^+$ depletion whereas even only partial CD4$^+$ depletion led to delayed rejection or indefinite survival.

Materials and methods

ANIMALS

Inbred male DA ($RT1^a$) and Lewis ($RT1^l$) rats aged 8–14 weeks were obtained from Manchester University Medical School Animal unit. BALB/c mice aged 6–8 weeks were bred in the same unit.

CORNEAL TRANSPLANTATION

Lewis strain donor rats were killed by cervical dislocation and 3 mm central corneal discs were scored by trephine. The removal was completed with corneoscleral scissors and the button, covered by balanced salt solution, was left in situ until required in order to minimise endothelial damage caused by excessive manipulation.

The technique used throughout the study was a modification of that described by Coster[14] and allowed retention of a non-irritant single suture with a buried knot. Recipient DA rats were anaesthetised with ether and 0·2 ml of diazepam solution (2 mg/l) was injected intraperitoneally. The right eye was anaesthetised with a drop of benoxinate 0·4% before a 3 mm trephine marked the recipient bed. The button was removed with microforceps and corneoscleral scissors. The prepared donor button was carefully manipulated into the bed and secured with 8–10 bites of a continuous 10/0 monofilament nylon suture placed intrastromally and tied into the wound with a triplicate knot cut flush to the surface. A single drop of chloramphenicol 0·5% was instilled.

POSTOPERATIVE MANAGEMENT

Animals were examined on the first postoperative day; those with surgical failures due to wound dehiscence, iris prolapse, and hyphaema were excluded from the study and killed. The remaining animals received a drop of chloramphenicol and were thereafter examined on alternate days. On day 3 postoperatively any opaque grafts were eliminated from the study because they were more likely to represent excessive mechanical damage to the donor material rather than immunological rejection. A final drop of chloramphenicol was then instilled.

CLINICAL OBSERVATION

Grafted animals were examined under anaesthesia on alternate days using a portable slit-lamp. The grafts were graded from 0–4 for opacity, oedema, and vascularity as previously described.[12] The day of rejection was recorded as that on which the combined score reached 6 or more.

STATISTICAL ANALYSIS

The survival times from transplantation until rejection were compared using the Mann Whitney test.

MONOCLONAL ANTIBODIES (mAb)

Ascites fluid from BALB/c mice injected with one of the following monoclonal producing hybridoma cell lines was collected in this laboratory: anti-CD4 (W3/25, OX35, OX38), anti-CD8 (OX8), anti-alpha/beta T-cell receptor (R73) (a kind gift of Professor Thomas Hunig, Würzburg). Radial immunodiffusion assays were used to estimate the immunoglobin (Ig) concentrations. For injection mAbs were diluted in phosphate buffered saline (PBS) and stored at −70°C in 1 ml aliquots.

CELLULAR DEPLETION IN VIVO

DA rats aged 10–12 weeks old received intraperitoneal injections of 1 ml of ascites containing 6 mg of OX8 (anti-CD8) mAb three times a week. A second group was treated three times a week with 1 ml of a cocktail containing two non-competing anti-CD4 mAbs, OX35 (0·75 mg) and OX38 (2·5 mg) which deplete CD4$^+$ T-cells.[15] The third group was injected three times a week with 1 ml of a non-reactive control mAb OX21 (anti-human C3b) that does not react with rat antigens. Treatment was continued for 48 days. On day 16 after the initial injection of mAb the animals received a penetrating allogeneic Lewis corneal graft into the right eye.

MONITORING OF DEPLETION

The ability of the antibody injections to deplete circulating cells was monitored at 7–10 day intervals by flow cytometry. Blood samples of 1 ml were obtained from the tail vein of each CD8$^-$ and CD4$^-$ depleted rat. After separation of leucocytes on a Ficoll density gradient (specific gravity 1·083), cells were washed and surface phenotyped. Leucocytes from the anti-CD8 treated rats were stained using a primary mouse anti-CD8 mAb (OX8) followed by fluorescein conjugated FITC-F(ab$'$)$_2$ rabbit anti-mouse IgG, which fluoresces green (Dako Ltd, High Wycombe, UK), containing 1% normal rat serum to block anti-rat Ig cross-reactivity. Leucocytes prepared from the anti-CD4 treated rats were double stained using a five-stage staining protocol (1) mAb R73 (anti-T-cell receptor); (2) FITC-F(ab$'$)$_2$ anti-mouse IgG in 1% normal rat serum; (3) blocked with W6/32 (mouse mAb non-reactive with rat); (4) biotinylated anti-CD4 mAb (b-W3/25); (5) phycoerythrin-streptavidin, which fluoresces red. Cells were held on ice and washed at each stage with PBS containing 2% fetal calf serum plus 0·02 M sodium azide to prevent capping of surface molecules, and finally fixed in 1% formaldehyde for flow cytometric analysis using the Beckton Dickinson FACS cell sorter. Using an optical to electronic coupling system, the flow cytometer records how the cell interacts with a laser beam in terms of the ability of the cell to scatter the incident light and to emit fluorescence. Dead cells and cell debris were excluded by electronic gating on forward and side angle light scatter. Analysis of 10^4 events was performed using the Consort 30 program.

IMMUNOHISTOCHEMISTRY

Corneoscleral buttons were removed and immediately frozen in liquid nitrogen. Serial sections of 5 μm thickness were cut across the central area of the graft and stained using an indirect immunoperoxidase technique. Normal rabbit serum was added to the sections to block non-specific antibody binding prior to mAb incubation. A panel of mouse mAbs (produced as supernatants of hybridoma cell cultures in this laboratory) was used: W3/25, OX8, R73, OX1 (anti-CD45, the leucocyte common antigen) or OX42 (anti-macrophage). Rabbit anti-mouse peroxidase conjugated secondary antibody (Dako Ltd) was added before development in diaminobenzidine and hydrogen peroxide and slides were counterstained with 50% haematoxylin solution.

A non-reactive culture supernatant (OX21) was applied to sections as a negative control and sections of normal rat spleen were used as a positive control.

Slides were examined by the same observer in a masked fashion on three separate occasions. Cell numbers were estimated in the mid stroma of the centre of the graft using a ×40 power objective and ×12·5 eye piece graticule.

Results

CELL DEPLETION STUDIES IN VIVO

Depletion of CD4$^+$ cells

CD4$^+$ T-cells are the majority of circulating T-cells in DA rats comprising 36·3 (SD 3·4)% of circulating leucocytes in untreated animals (Fig 1A). Monoclonal antibody therapy reduced this to 13·6 (SD 2·8)% within a week but further depletion did not occur in the majority of animals, despite continuing antibody treatment, until day 51 when a sudden dramatic decline in cell numbers to 4·9 (SD 1·0)% occurred (Table 1A). However two animals demonstrated virtually complete depletion of CD4$^+$ cells by day 14 and double staining demonstrated that most of the circulating T cells were CD8$^+$ at this stage.

Depletion of CD8$^+$ cells

CD8$^+$ T-cells comprise 23·9 (SD 0·7)% of the

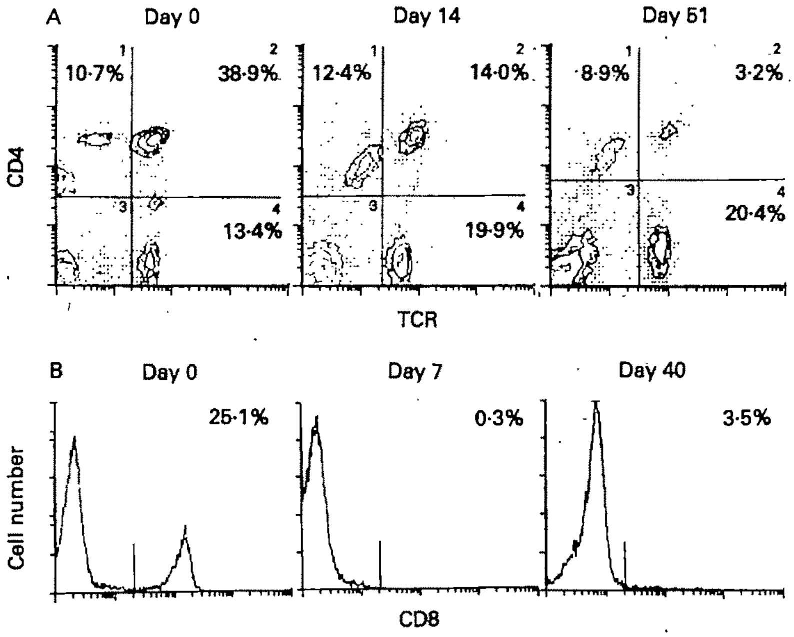


Figure 1 Flow cytometry profiles of peripheral blood leucocytes prepared from a DA rat before treatment (day 0) and during treatment with mAb therapy. (A) Flow cytometry profiles of peripheral blood leucocytes of a DA rat double stained for the T-cell receptor, TCR, (with R73 mAb, fluorescing green, x axis) and CD4 (with W3/25 mAb, fluorescing red, y axis). Four distinct populations of cells were identified on the basis of the intensity of fluorescence, which is proportional to the density of each of the expressed cell surface antigens that were marked. T-cells (TCR+) fluorescing strongly in the green are located in quadrants 2 and 4. CD4$^+$ cells fluorescing red are located in quadrants 1 and 2. The double stained CD4$^+$ T-cells are represented in quadrant 2 and comprise 38·9% of the peripheral blood leucocytes in the untreated rat (day 0). Regular mAb therapy depleted the CD4$^+$ T-cells to 14% on day 14 and 3·2% on day 51. (B) Flow cytometry profiles of leucocytes from a DA rat single stained for CD8 (with OX8 mAb). The number of cells (y axis) is plotted against the amount of fluorescence on the x axis with a vertical line drawn at the point which no negatively stained cells were found. Thus non-staining cells are to the left of this line and cells staining for CD8 are found to the right, the percentage of these positively staining cells is indicated on the diagram and shows CD8$^+$ cells comprising 25·1% of the circulating leucocytes before anti-CD8 treatment (day 0) and almost complete depletion of CD8$^+$ cells on days 7 with a small recovery by day 40.

peripheral blood leucocytes in normal DA rats (Fig 1B). Thrice weekly monoclonal antibody therapy reduced this to 0·7 (±0·2)% after 1 week, but cell numbers recovered to reach 8·0 (SD 2·9)% by day 40 despite continuing treatment (Table 1B).

CORNEAL ALLOGRAFT SURVIVAL IN DEPLETED RECIPIENTS

Untreated allograft recipients

Of 11 DA rats bearing Lewis allografts three technical failures were excluded from the study. All the remaining eight grafts were rejected between 7 and 21 (median 12) days.

Control (OX21) treated recipients

One graft was a technical failure and the animal was killed. The other six rats rejected their Lewis graft between 7 and 21 (median 12) days with no difference compared to the survival times of grafts in injected recipients (Fig 2A).

Table 1 Depletion of CD4$^+$ and CD8$^+$ cells in peripheral blood in mAb treated, corneal allografted DA rats

(A) The means (standard errors) of CD4$^+$ staining cells in the anti-CD4 treated animals.						
Day of treatment:	0	7	14	23	37	51
% of CD4$^+$ cells:	36·3 (3·4)	13·6 (2·8)	10·8 (2·4)	10·2 (1·0)	7·5 (0·6)	4·9 (1·0)
(B) The means (standard errors) of CD8$^+$ cells in the anti-CD8 treated animals.						
Day of treatment:	0	8	14	22	40	
% of CD8$^+$ cells	23·9 (0·7)	0·7 (0·2)	3·5 (0·6)	6·2 (1·1)	8·0 (2·9)	

The percentage of blood leucocytes that stained were either CD4$^+$ or CD8$^+$ is shown against the day of treatment. The day of the first treatment is day 0 and the rats were grafted on day 16.

Anti-CD8 (OX8) treated recipients

The six allografts were rejected between 7 and 27 days with a median rejection time of 12 days. There was no difference in the rejection times compared with graft rejection in the OX21 treated controls (Fig 2B).

Anti-CD4 (OX35/OX38) treated recipients

Six technically successful allografts were followed for 100 days. There was a significant delay in rejection times compared with the OX8 or OX21 treated recipients ($p<0·01$, Mann Whitney test). Four of the grafts were rejected between 13 and 35 (median 22 days) while the remaining two grafts failed to be rejected after 100 days despite cessation of mAb therapy on day 50 (Fig 2C).

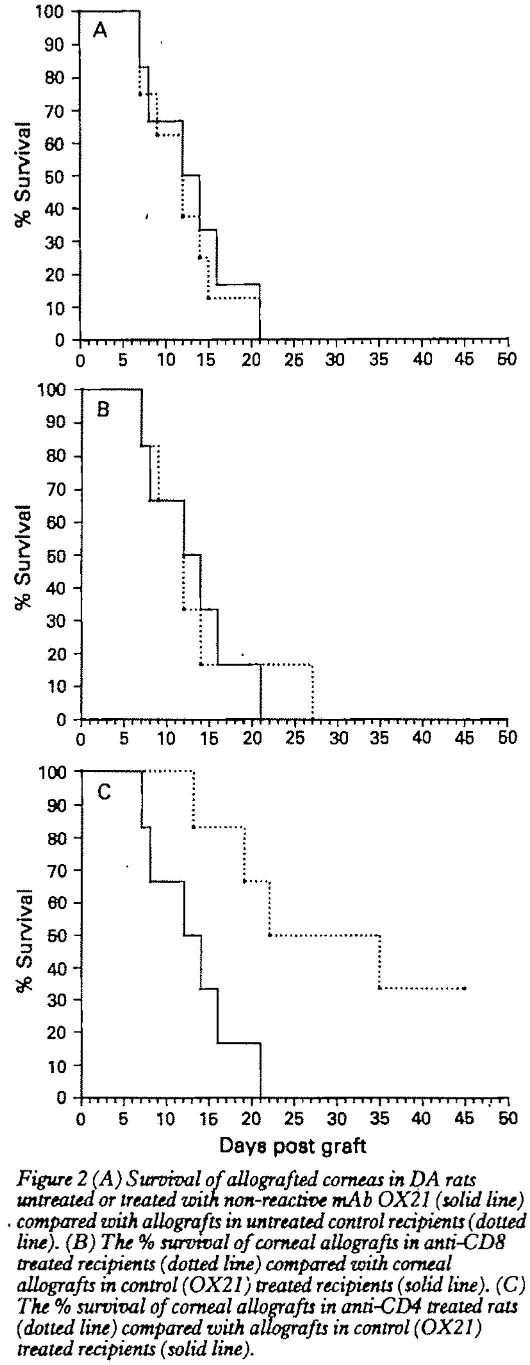


Figure 2 (A) Survival of allografted corneas in DA rats untreated or treated with non-reactive mAb OX21 (solid line) compared with allografts in untreated control recipients (dotted line). (B) The % survival of corneal allografts in anti-CD8 treated recipients (dotted line) compared with corneal allografts in control (OX21) treated recipients (solid line). (C) The % survival of corneal allografts in anti-CD4 treated rats (dotted line) compared with allografts in control (OX21) treated recipients (solid line).

Figure 3 (A) Vascularised, opaque rejected Lewis corneal allograft in an untreated control DA recipient. (B) A non-rejected long term surviving clear Lewis corneal allograft in a DA recipient depleted of CD4$^+$ cells by regular mAb therapy.

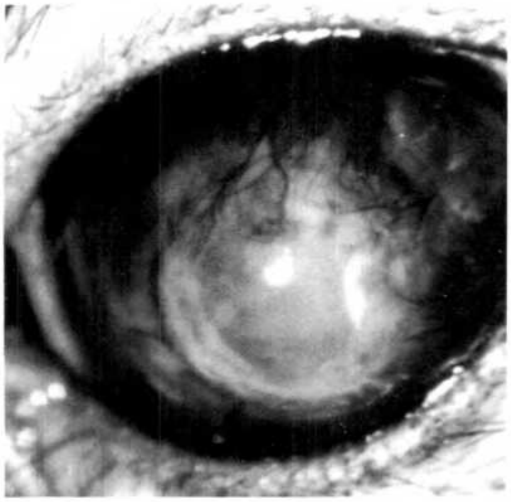


Fig 3A

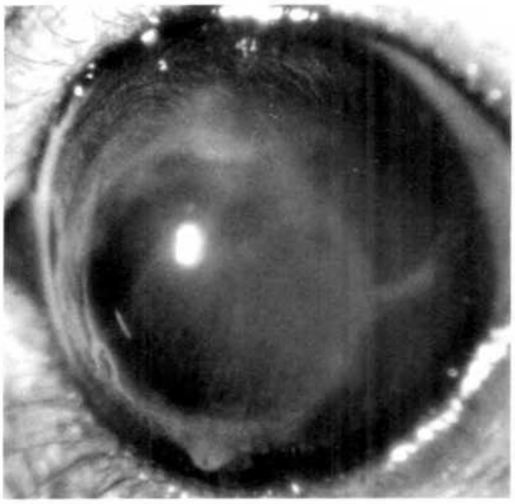


Fig 3B

There was no correlation between the amount of CD4$^+$ cell depletion at the time of grafting and the eventual graft survival.

Rejected allografts became opaque and vascularised and, though after several weeks the opacity partially cleared, the grafts remained vascularised (Fig 3A). In contrast, the long term surviving grafts remained clear and though vessels grew up to the wound they did not grow onto the graft (Fig 3B).

Histology of grafts

Syngeneic grafts had low numbers of infiltrating leucocytes staining for the leucocyte common antigen CD45 (OX1) and most of these appeared to be macrophages marked by OX42. Rejected grafts in the untreated, CD4$^+$ depleted, and CD8$^+$ depleted animals had a heavy infiltration of macrophages staining with OX42 (Fig 4) but all showed low numbers of T-cells and very few CD8 (OX8$^+$) cells present. There was a less heavy infiltration of macrophages in rejected grafts from the CD4-depleted animals compared with the untreated controls or CD8-depleted animals.

Discussion

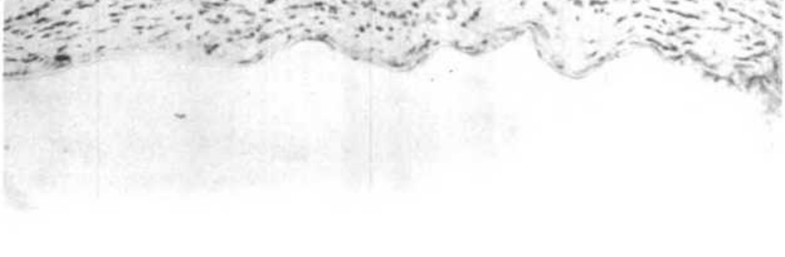
The mechanism of destruction of allogeneic tissue is unknown[4] and this applies to corneal grafts. Although T-cells are required for the afferent limb of the corneal allograft response,[5] the precise effector mechanism of corneal graft rejection remains an enigma. Using selected mAbs and frequent administration it was possible to deplete T-cell subsets and this enabled an examination of their roles in corneal allograft rejection in vivo.

CD8$^+$ cells are important effector cells in immune responses, particularly viral infections and depletion of cells by anti-CD8 mAbs has been shown to modify the outcome of viral encephalitis.[13] They have also been presumed to be important in corneal allograft rejection; indeed, in vitro evidence using spleen cells obtained from animals with rejected corneal allografts implicates the cytotoxic CD8$^+$ T-cell as the major effector cell.[6] However the results of the present study suggest that this may not reflect the mechanism of corneal allograft rejection in vivo because animals depleted of CD8$^+$ cells rejected corneal allografts in the same tempo as controls. This result, although initially surprising, is in fact in keeping with other experimental models where depletion of CD8$^+$ cells failed to modify allograft rejection in skin and heart allograft models.[7,16,17] Despite 96–100% depletion of circulating CD8$^+$ cells at the time of grafting we also failed to influence corneal graft rejection.

In contrast, results presented in this study show that pretreatment of DA rat recipients for 2 weeks with murine anti-CD4 mAbs led to significantly prolonged corneal allograft survival or even tolerance.

Depletion of CD4$^+$ cells is notoriously difficult[15] and different anti-CD4 mAbs vary in their ability to deplete. The mAb W3/25 reacts with CD4 but fails to deplete, whereas a cocktail of OX35 and OX38 depletes CD4$^+$ cells very effectively after 6 weeks of treatment.[15] One difficulty has been that the CD4 molecule is expressed on other cells such as macrophages as well as on T-cells.[18] In the present investigation the depletion of CD4 T-cells was determined by double staining for CD4 and the alpha-beta TCR. Depletion of CD4$^+$ T-cells from 36% to $<$10% of peripheral blood lymphocytes correlated with a delayed rejection of corneal

Figure 4 Immunoperoxidase staining with mAb OX42 in a section from the centre of a rejected graft in the anti-CD8 depleted group showing heavy infiltration of macrophages.



allografts in this group. It may be that grafting after 6 weeks of treatment when greater depletion of CD4+ cells is obtained may allow better survival of corneal allografts and this is being investigated.

If the CD8$^+$ cytotoxic T-cell is not required for allograft rejection in vivo then several optional candidates remain. The possibilities that antibodies,[19] natural killer cells,[20] or macrophages[11 12] are involved in the effector mechanism of corneal graft rejection have received some attention. It is also possible that cytotoxic CD4$^+$ T-cells are involved but there is no direct evidence for this. Their low numbers in the rejecting corneal grafts and the overwhelming infiltration of macrophages even in CD4$^+$ and CD8$^+$ depleted recipients suggest that the latter may in fact play the major role in tissue damage, in a local delayed-type hypersensitivity reaction.[21] The role of the CD4$^+$ T-cells is more likely to be concerned with the recognition of alloantigen presented on antigen presenting cells which explains the specificity of the rejection response. Antigen presentation may occur locally in the limbus and ocular Langerhans cells have been shown to be capable of presenting antigens to T-cells.[22] Cytokine release by the alloreactive T-cells may activate effector cells, possibly macrophages, locally within the graft leading to graft damage and opacity. Failure to recognise alloantigen in syngeneic grafts or depletion of CD4$^+$ cells by mAb does not lead to activation of the effector mechanisms and the corneal grafts remain clear.

As well as increasing understanding of corneal allograft rejection this study suggests that treatment of high risk recipients with anti-CD4 antibodies may have important clinical applications.

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Type IV collagen and laminin in Bruch's membrane and basal linear deposit in the human macula

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Abstract

Tissue obtained from the macula in 10 human eyes (53–77 years) was used for an investigation into the extracellular matrices of the retinal pigment epithelium (RPE), Bruch's membrane, and the choriocapillaris. The ultrastructural distribution of type IV collagen and laminin was documented using immunogold labelling. Labelling for type IV collagen was strongly positive in all the specimens in the basement membranes of the choriocapillaris but not that of the RPE where labelling was either weak or absent. Laminin was localised to deposits of granular material in Bruch's membrane but was absent from the basement membrane of the RPE and the choriocapillaris. Basal linear deposit, observed in three cases, demonstrated labelling for laminin but not for type IV collagen. The series was too small for correlation of these morphological changes with age.

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Vision can be affected in the elderly by a variety of pathological changes which interfere with the function of the retinal pigment epithelium (RPE) and the maintenance of the photoreceptors. Photoreceptor atrophy occurs when an abnormal extracellular matrix – for example, drusen, accumulates between the pigment epithelium and Bruch's membrane. Drusen are clinically well recognised and can be classified as hard, soft, calcified, and diffuse according to histological criteria.[1] However, a morphological distinction can be made between drusen and basal linear deposit. Various authors[2-4] have used the term 'basal linear deposit' for an accumulation with specific appearances (after PAS and Mallory trichrome stains) beneath the RPE. The precise biochemical composition of the basal linear deposit is not known and identification of the constituents is essential to an understanding of the pathogenesis of age-related macular degeneration.

Studies using transmission electron and light microscopy have adequately documented the morphology of the age-related changes in Bruch's membrane.[2 5-8] The initial change is an accumulation of vesicles and granular and filamentous material in the inner collagenous zone. This accumulation progressively increases with age until it occupies both collagenous zones. Various attempts have been made to determine the biochemical nature of the age-related deposits in Bruch's membrane outside the macular region[9-13] but it is not known if their accumulation is the cause or the result of RPE dysfunction. Since Bruch's membrane may act as a selective barrier to the movement of molecules from the choroidal circulation to the outer retina,[14] alterations in its composition could have important physiological consequences.

Age-related thickening and degeneration in Bruch's membrane,[7 15] drusen formation,[16] and basal linear deposits[3] each appear to provide a matrix which stimulates ingrowth of macrophages and endothelial cells. Vascular ingrowth is an important complication of age-related macular degeneration and is a major cause of blindness in the elderly population of the Western world.[17 18] Bruch's membrane acts as a barrier to subretinal neovascularisation and breaks in this structure significantly increase the incidence of growth of new vessels.[7] The differences between the factors causing senile degenerative atrophy and disciform degeneration are poorly understood.[4] It is now accepted that type IV collagen and laminin are matrix constituents which facilitate endothelial cell movement in vitro.[19-22] Thus knowledge of the precise biochemical composition of the age-related deposits in Bruch's membrane will allow an evaluation of their potential influence on vascular ingrowth in disciform degeneration. As early forms of basal linear deposit have ultrastructural similarities to basement membrane[2] it was considered likely that the deposit would contain type IV collagen and laminin which are the principal components of many basement membranes. In this study we investigated the fine structural distribution of collagen type IV and laminin in Bruch's membrane of aged human macula.

Materials and methods

Normal aged macular tissue was obtained both from freshly enucleated eyes of five uveal melanoma patients, a patient with a corneal ulcer, and from four postmortem eyes. The age range of the subjects was between 53 and 77 years (Table 1). Routine macroscopic and microscopic examination excluded the presence of any secondary disease process which could have affected macular morphology.

Surgically enucleated eyes were fixed

Table 1 Clinical details of surgical enucleations and postmortem eyes

Case no	*Age*	*Sex*	*Indication for enucleation*	
1	53	F	CBM	
2	54	F	CBM	
3	58	M	PM	
4	59	M	PM	
5	60	M	PM	
6	64	M	PM	BLD
7	71	F	PM	BLD
8	73	M	CM	BLD
9	75	F	CBM	
10	77	F	CM	

CBM=ciliary body melanoma; CM=choroidal melanoma; PM=postmortem; BLD=basal linear deposit.

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immediately after enucleation in freshly prepared fixative of 4% paraformaldehyde (PFA) plus 0·2–1·0% glutaraldehyde in 0·1 M Sorensen's phosphate buffer or cacodylate buffer (pH 7·4) with 5% sucrose added; details of fixation are provided elsewhere.[23] The postmortem eyes were obtained from the Greek Eye Bank (University Department of Ophthalmology, Thessaloniki) and fixed within 1·5 to 9 hours of death following removal of the cornea for transplantation. Fixation was achieved with 0·5% glutaraldehyde plus 4% formalin in phosphate buffer pH 7·4 at room temperature for 2 hours. Details of the medical and ocular history of the postmortem cases were obtained from close relatives and subsequent macroscopic examination revealed a normal macula and disc.

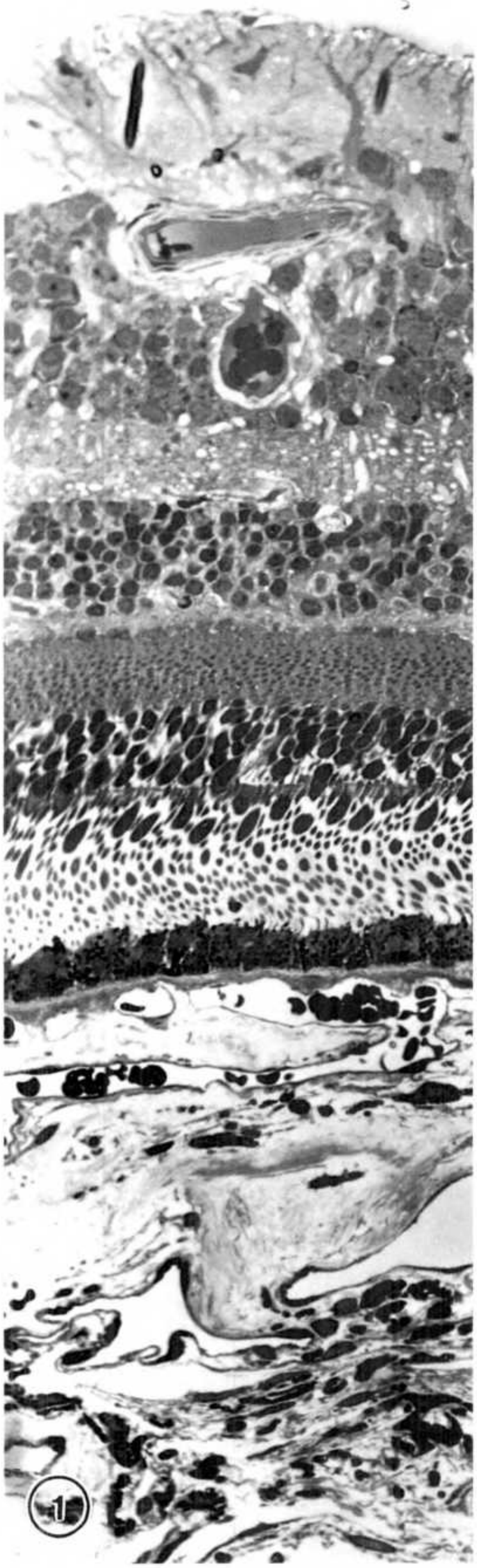

Figure 1 The paramacular area in a 53-year-old female with a ciliary body melanoma. The choroidal vessels are thin-walled and Bruch's membrane is not thickened (toluidine blue, ×24).

The macula region was dissected from each eye and in the majority of cases the retina remained attached. Radial blocks were taken and processed for London resin white (LR white) embedding and cryoultramicrotomy.[23] LR white is a hydrophilic resin that is used for immunocytochemical studies owing to its property of preserving tissue antigenicity.[24]

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Polyvalent goat antibodies against type IV collagen were raised against human and bovine type IV collagen and supplied by Southern Biotechnologies (Bionuclear Services Ltd). The antibody was affinity purified and cross absorbed against types I, II, III, and V collagen which were purified from human tissue. The specificity of this antibody to human type IV collagen has been confirmed by the supplier using indirect enzyme linked immunosorbent assay (ELISA).

Polyvalent rabbit antibodies against laminin were supplied by Heyl (Germany) and had been raised in rabbits by multiple injections of human laminin. The serum has been tested by the supplier with the following immunological assays: ELISA, immunoblot, and immunohistology (fluorescence, APAAP). The antibody dilutions in Tris buffer plus 1% BSA, determined by previous experimental work, were between 1:40 and 1:150 for type IV collagen and laminin antibodies at dilutions between 1:30 and 1:100. These antibodies have been successfully employed in our laboratory for immunogold electron microscopic studies of various ocular tissues.[25-28] The precise immunocytochemical procedure has been described by Marshall *et al*.[27]

CONTROLS

Negative controls comprised substitution of the primary antiserum with normal goat and rabbit serum (Sigma) at the same dilutions. Retinal vessels were used as an internal positive control (within the same tissue section) for type IV collagen which is located in the basement membranes within the vessel wall.[25] The basement membranes of the ciliary epithelium were used as an external positive control for type IV collagen and laminin.[28 29] We consider internal positive controls to be even more reliable than external positive controls from another tissue block.

Our criteria for positive localisation required the restriction of immunogold particles to discrete structures. Labelling was considered to be non-specific if a significant number of immunogold particles were present on internal negative controls. Internal negative controls comprised cell nuclei, mitochondria, pigment granules, and red blood cells: on the basis of previous investigations these had been found to be the first structures to exhibit non-specific labelling.

Results

The use of different concentrations of glutaraldehyde in surgically enucleated eyes did not alter the pattern or intensity of immunogold labelling for type IV collagen and laminin. The quality of preservation of cells in postmortem specimens was poorer than that in surgically enucleated eyes, but in all the specimens the structure was morphologically satisfactory by light microscopy (Fig 1). The addition of 5% sucrose to the cacodylate buffer eliminated the previously documented superiority of phosphate buffer in ultrastructural preservation.[26]

There was no apparent difference in immunolabelling of collagen type IV and laminin when comparing sections from LR white processed tissue with ultrathin sections of frozen tissue. LR white embedding was predominantly used because it was much less technically demanding than cryoultramicrotomy and more satisfactory in terms of preservation of ultrastructure in the material used in the present study. Our previous studies in aged ocular tissues have demonstrated similar results with both techniques for laminin and type IV collagen. Therefore for the study of laminin and type IV collagen, LR white embedding was considered the technique of choice. The employment of both techniques served to consolidate the results. However, the illustrations for the present communication were prepared from LR white embedded material.

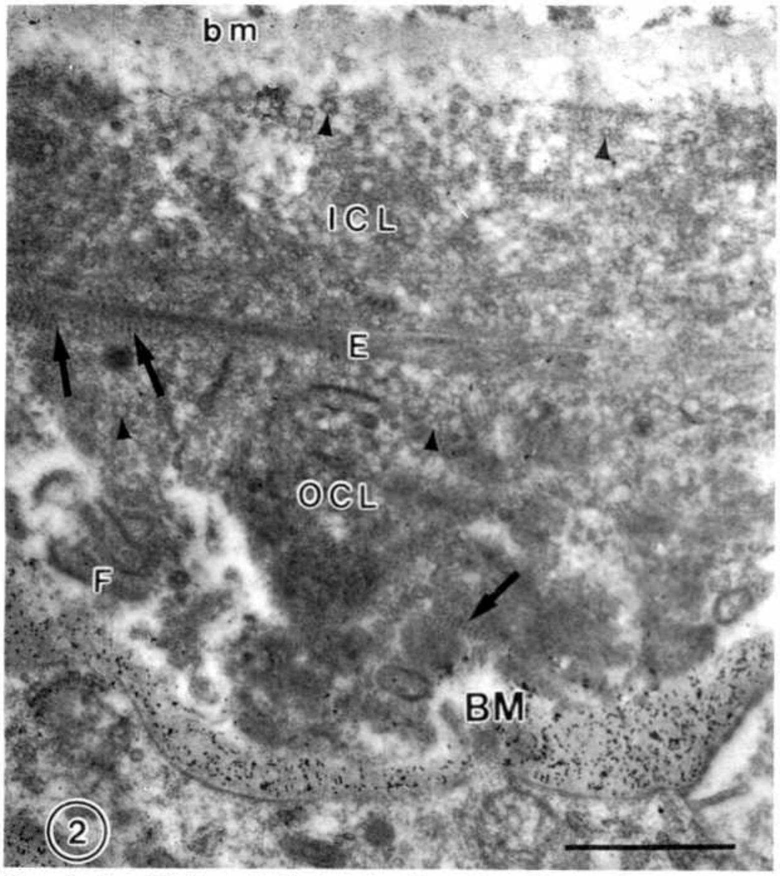

Figure 2 Type IV collagen distribution in Bruch's membrane. Immunogold particle density over the RPE basement membrane (bm) is considerably less than that over the basement membrane (BM) of the choriocapillaris. A small amount of type IV collagen is also present in the inner collagenous layer (ICL), the elastic layer (E), and the outer collagenous layer (OCL), that of the elastic layer occurring in a space between elastic fibrils. Note association of fibrous banded material with elastic layer as well as its presence in the outer collagenous layer (arrows). Coated vesicle-like bodies can be seen in both the inner and outer collagenous layers (arrowheads). Coated membrane fragments (F) are restricted to the outer collagenous layer (bar=1 μm).

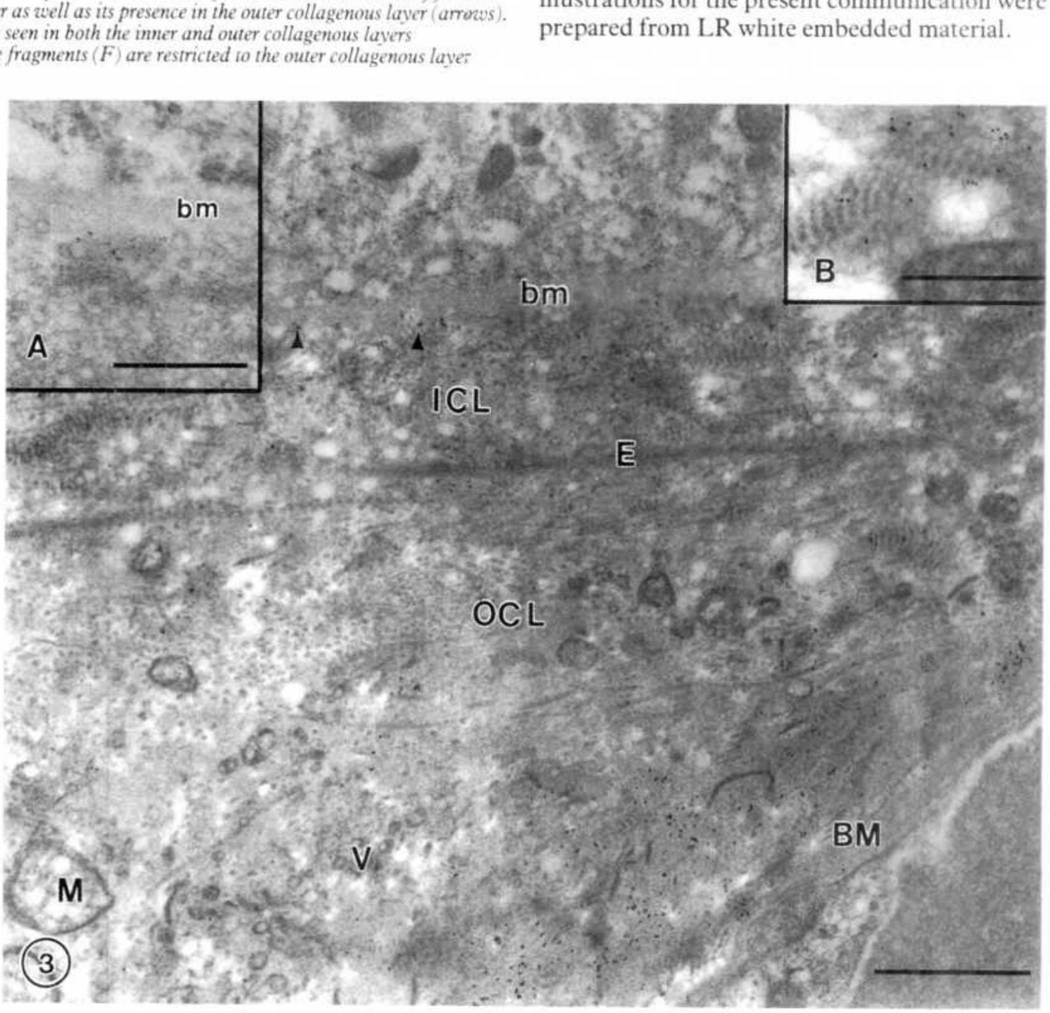

Figure 3 Fine structural localisation of laminin in Bruch's membrane. Immunogold particles are absent from the basement membranes of the RPE (bm) and the choriocapillaris (BM). Some degree of labelling is present in the inner collagenous layer (ICL) particularly at its interface with the RPE basement membrane (arrowheads). Note the absence of immunogold particles from the elastic layer (E). Labelling of the outer collagenous layer (OCL) is concentrated mainly to granular deposits in the region of its interface with the choriocapillary basement membrane (BM). Coated vesicle-like bodies (V) and coated membrane bound bodies (M) are free of label (bar=1 μm.) Inset A: Laminin labelling at the interface between the RPE basement membrane (bm) and the inner collagenous layer was often restricted to small electron dense plaques (bar=1 μm). Inset B: Immunogold particles localising laminin are largely restricted to the periphery of fibrous banded material (bar=0·5 μm).

NOMENCLATURE

In the description of type IV collagen and laminin distribution in Bruch's membrane we have adopted the nomenclature proposed by Killingsworth[5] to classify the various deposits associated with aging of Bruch's membrane. According to this classification 'coated vesicle-like bodies' are circular bodies composed of a single membrane lining an electronlucent core and occurring in two sizes (70 nm and 110 nm). 'Coated membrane-bound bodies' (400 to 2500 nm diameter) contain fine granular material, droplets, and coated vesicle-like bodies. 'Coated membrane fragments' are thought to be the remnants of ruptured coated membrane-bound bodies.[5]

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Basement membrane of the RPE

In some specimens the basement membrane of the RPE exhibited weak labelling with type IV collagen antibodies (Fig 2) but this finding was not uniform in all the cases studied as labelling was absent from other specimens. Such variation in labelling could not be related to the source of tissue (that is, surgical enucleations or post-mortem specimens) nor to the concentration of fixative employed. The most surprising finding was that laminin was not identified in the RPE basement membrane in any of the specimens investigated (Figs 3–6).

Bruch's membrane

A small amount of labelling for type IV collagen was present in the inner collagenous layer, the elastic layer, and the outer collagenous layer of Bruch's membrane. This was a consistent feature in all the specimens studied. Although labelling was present in the elastic layer, immunogold particles were not located to the elastic fibres but rather to the matrix surrounding these fibres (Fig 2). Immunogold labelling for type IV collagen was absent from coated vesicle-like bodies, coated membrane bound bodies, coated membrane fragments, and fibrous banded material. Laminin was localised to deposits of fine granular-like material present in the inner collagenous layer. More frequently laminin was dispersed within the fine granular-like material between the outer collagenous layer and the basement membrane of the choriocapillaris (Fig 3). Small discrete patches of laminin labelling were also observed in the inner collagenous layer immediately adjacent to the RPE basement membrane (Fig 3, inset A). These patches of labelling were spaced in a manner which was almost regular. The only difference in the structure of these patches and the inner collagenous layer was a small augmentation in electron density.

Laminin was also associated with the periphery of fibrous banded material present within Bruch's membrane, labelling being generally absent from the actual striations of this material (Fig 3, inset B). We considered that fibrous banded material was quite distinct from long-spacing collagen in its location, structure, and periodicity. Long-spacing collagen was present between the outer collagenous layer and the basement membrane of the choriocapillaris. Fibrous banded material was located within both the inner and outer collagenous layers and sometimes in association with the elastic layer (Fig 2).

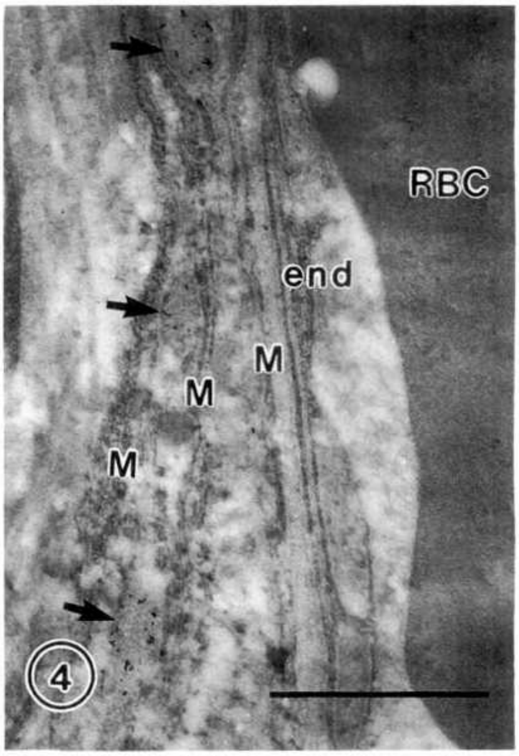

Figure 4 Laminin distribution in major blood vessel in the choroid. Laminin localised to discrete clumps of granular-like material (arrowed) between the three layers of myocytes (M) within the vessel wall. Note absence of label from red blood cell (RBC). (end=endothelium of blood vessel (bar=1 μm).

In contrast with long-spacing collagen, fibrous banded material had a significantly shorter periodicity and lacked the fine structure of the latter. No association of laminin was seen with long spacing collagen within Bruch's membrane. Similarly, laminin was absent from the elastic fibres in the elastic layer (Fig 3).

Choriocapillaris

There was considerable degree of variation in the thickness of the basement membrane of the endothelial cells and this could not always be attributed to the plane of section of the choriocapillaris. Type IV collagen was clearly localised to the basement membranes around the circumference of the choriocapillaris and labelling was present throughout the entire width of the basement membrane. In contrast to the RPE basement membrane, the basement membrane of the choriocapillaris exhibited intense labelling with type IV collagen antibodies (Fig 2). Antibody labelling for laminin was so sparse as to be regarded as negative.

Choroidal stroma

Type IV collagen and laminin were localised to the basement membranes of the large choroidal vessels. Type IV collagen was also localised to all basement membranes present in the stroma, some of which were not associated with cells but

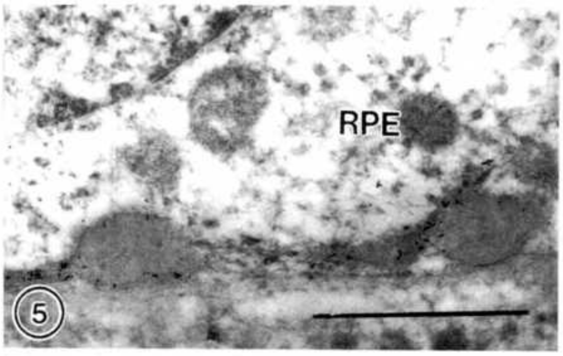

Figure 5 Immunogold localisation of laminin in early form of basal linear deposit. Labelling is restricted to the circumference of this amorphous basement membrane-like material which has not yet separated the retinal pigment epithelium (RPE) from its basement membrane (bar=1 μm).

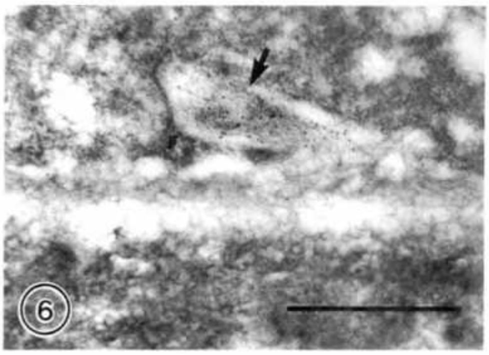

Figure 6 Laminin present within filamentous form of immature basal linear deposit (arrowed) (bar=1 μm).

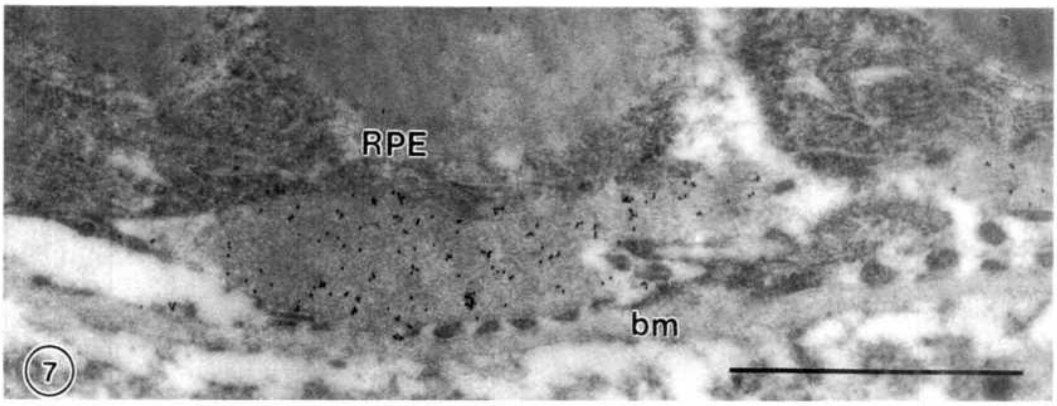

Figure 7 Early stage basal linear deposit exhibiting granular-like morphology is labelled throughout with antilaminin antibodies. Note numerous basal infoldings separating deposit from basement membrane (bm) of retinal pigment epithelium (RPE). Note absence of laminin from RPE basement membrane (bar=1 μm).

were lying free amongst collagen fibrils of the stroma. Small isolated deposits of fine granular material, similar in appearance to basal linear deposit (see below), were occasionally seen in the stroma between large blood vessels and were positive for laminin (Fig 4). Elastic fibres within the walls of large blood vessels were free of immunogold particles for laminin or type IV collagen. Considerably larger deposits of granular material similar to those observed in Bruch's membrane were frequently present in the intercapillary zone. These deposits appeared to be associated with choroidal stroma rather than the outer collagenous layer.

Basal linear deposit

Basal linear deposit was observed in three out of the 10 specimens (cases 6–8, see Table 1). Small sized basal linear deposit could be divided into three types on the basis of their morphological appearance: basement membrane-like, granular-like, and filamentous-like. These deposits were within basal infolds and were not accompanied by a separation of the RPE from its basement membrane. Two distinct labelling patterns of these deposits were then noted with laminin antibodies. Labelling for laminin was restricted to the margins of the basement membrane-like basal linear deposit (Fig 5) but was present throughout the entire matrix of the granular-like (Fig 6) and fine fibrillar-like structures (Fig 7).

Larger forms of basal linear deposit contained a mixture of basement membrane-like, fine granular-like, and fine fibrillar-like material. These deposits were invariably accompanied by a separation of the RPE from its basement membrane (Fig 8). The labelling pattern of the large deposits for laminin was similar to that of the small deposits: the margins of basement-like material and the entire matrix of the fine granular-like and fine fibrillar-like material were labelled (Fig 8). Laminin was absent from profiles of long-spacing collagen associated with

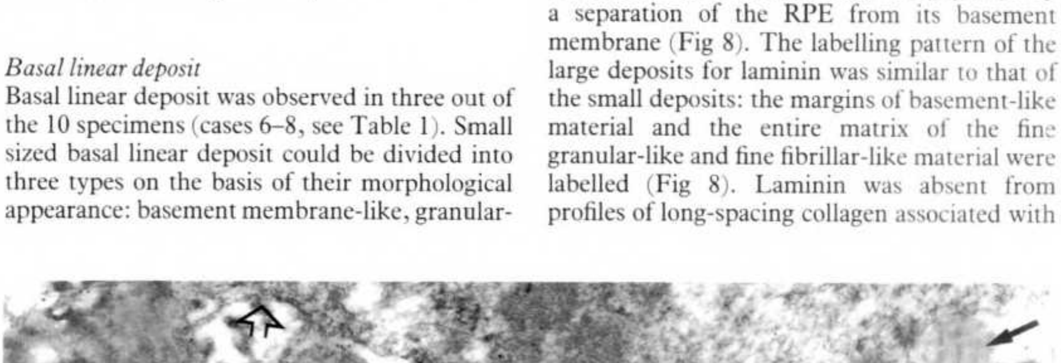

Figure 8 More advanced form of basal linear deposit labelled with laminin antibodies. Immunogold particles are over filamentous/granular material, but are absent from amorphous basement membrane-like material. Note absence of labelling from RPE basement membrane (bm) and long-spacing collagen (arrowed). The cell basement membrane is shown by arrowheads. ICL=inner collagenous layer, RPE=retinal pigment epithelium (bar=1 μm).

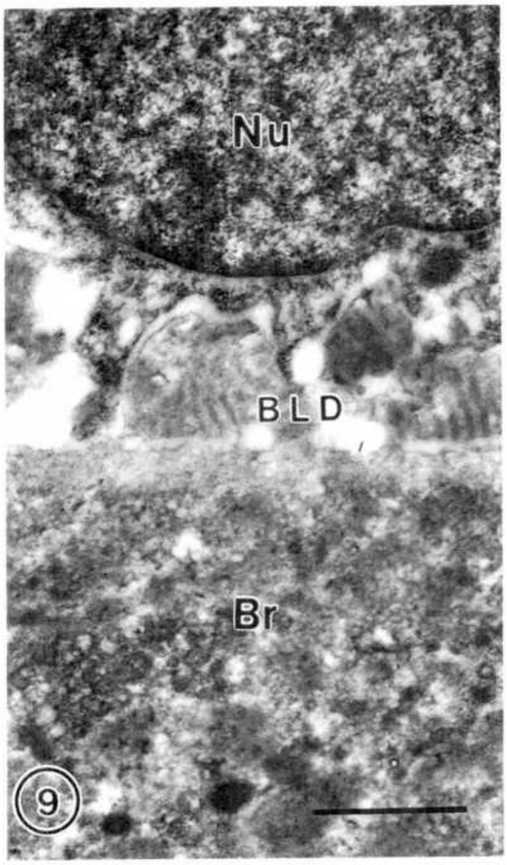

Figure 9 Normal rabbit serum control. Note lack of immunogold particles from basal linear deposit (BLD) and cell nucleus (Nu). Some non-specific labelling is present in Bruch's membrane (Br) (bar=1 μm).

these large basal linear deposits (Fig 8). Immunogold labelling for type IV collagen was not associated with any of the basal linear deposits described above.

CONTROLS

Immunogold labelling was sparse and non-specific in both the normal goat serum and normal rabbit serum negative controls (Fig 9). Non-specific labelling tended to be greater in normal rabbit serum controls than in normal goat serum controls. Type IV collagen was demonstrated in the basement membranes of the retinal vessels (internal positive control). In the ciliary body control tissue, collagen type IV and laminin were observed on the basement membranes of the pigmented and non-pigmented ciliary epithelium (Fig 10). Laminin was also localised to zonular fibres arising from the ciliary body.

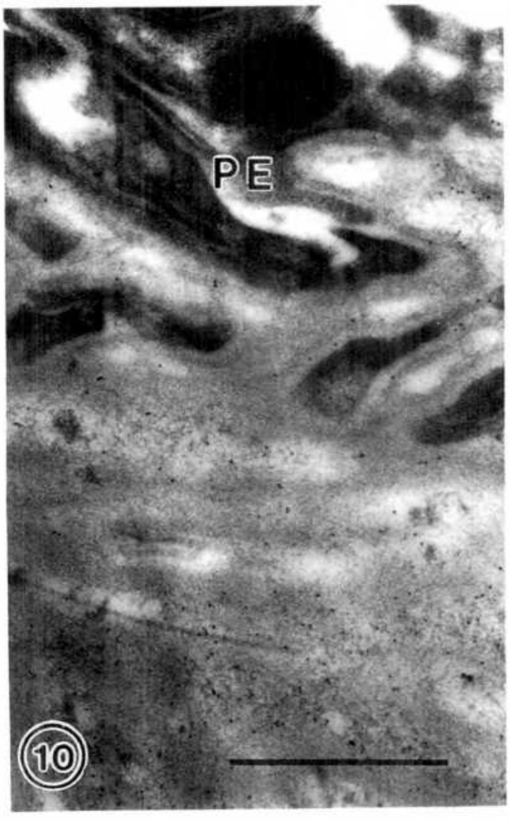

Figure 10 External positive control for laminin. Immunogold particles are distributed throughout the basement membrane of the pigmented ciliary epithelium (PE) (bar=1 μm).

Discussion

MACULA

Previous studies have been conducted on the distribution of collagen type IV and laminin in Bruch's membrane of the human eye[10-12] but have not referred to the macular region. To the best of our knowledge the present study is the first to concentrate on normal aged human macula. The importance of the macula in retinal disease merits separate consideration and this study is intended to provide baseline information for further investigation of age-related macular degeneration. It cannot be assumed that the distribution of extracellular matrix components in the macular choroid and RPE is identical to that of the extramacular regions, particularly since there are obvious differences in functional anatomy.

CHOROID

The overall distribution of type IV collagen seen in our aged macular tissue was similar to that of Das *et al*[11] in their fine structural immunogold study of extramacular human tissue. In their study and the present study labelling was more intense in the basement membrane of the choriocapillaris when compared with that of the RPE basement membrane. A similarity was also observed in the small amount of labelling of the collagenous layers.

Das *et al*[11] also localised laminin to the choriocapillary and RPE basement membranes but labelling was 'far less intense than that seen with type IV collagen'. In our study laminin labelling of these two basement membranes in the macular region was of insufficient intensity to be considered as positive. Laminin, a large multidomain glycoprotein, is a major structural basement membrane component[30] and numerous biological functions of basement membranes are controlled by its presence.[19 20] However, although collagen type IV, laminin, nidogen, and heparan sulphate proteoglycan are the best known components of basement membranes, the molecular architecture of basement membranes is incompletely understood.[30] In addition, a variation in composition has been demonstrated in basement membranes from different sites.[30] The localisation of laminin both to discrete structures within Bruch's membrane and to basal linear deposit is unique to the present study.

Light microscopic immunohistochemistry of human choroid indicated the presence of both type IV collagen and laminin in Bruch's membrane.[10 12] Newsome *et al*,[10] in an immunofluorescene study, stated that there was a bilaminar staining pattern for these two components. Unfortunately, the lack of resolution with immunofluorescent labelling does not permit a distinction between the constituent layers of Bruch's membrane. The bilaminar immunofluorescent pattern can be explained by an early deposition of basal linear deposit on the basal aspect of the RPE cells and in granular deposits in close apposition with the choriocapillaris as demonstrated by electron microscopy in the present study. There are a large number of alternative explanations for the differences in results obtained by immunocytochemistry, such as loss of antigenicity due to fixation, relocation of antigen in unfixed material, and differences in antibody specificity.

BASAL LINEAR DEPOSIT

Various types of drusen and basal linear deposit have been recognised histopathologically but clinicopathological correlations have been sparse.[1] At present no satisfactory classification exists and identification of the constituents of these deposits may elucidate their origin. Disciform macular degeneration represents a response of the posterior pole tissues to pre-existing disorder of the subretinal structures. For example, one proposal is that the process leading to disciform degeneration begins with thickening of the inner aspect of Bruch's membrane owing to synthesis of abnormal basement membrane-like material.[1]

Though basal linear deposit,[3] or alternatively, diffuse soft drusen,[31] has been recognised by light microscopists for many years and the fine structure was first described in 1964 by Lerche,[32] the nature remains enigmatic. Sarks[3-4] suggested that basal linear deposit represents a progressive disturbance in the metabolism of the RPE and that it may exert an influence on vascular ingrowth in disciform degeneration.[3] In its earliest form basal linear deposit is similar in morphology to basement membrane material and it is acceptable to speculate that basal linear deposit is a secretory product of RPE cells.[2] In more advanced stages basal linear deposit appears to be augmented by cellular deposit derived mainly from RPE cell membranes[2] and long-spacing collagen.[33] The association of laminin with two constituents of basal linear deposit was clearly demonstrated in the present study. Though in this investigation early forms of basal linear deposit possessed a similar morphology to that of basement membranes, type IV collagen was absent from these deposits. Thus basal linear deposit was biochemically distinct from the RPE basement membrane since the latter structure possessed a variable amount of type IV collagen but not laminin.

Laminin was a component of all forms of basal linear deposit which was observed between the RPE cell membrane and its basement membrane. Since laminin is an extracellular product as distinct from a cellular constituent, it can be concluded that early forms of basal linear deposit are quite distinct from a mere deposition of cell breakdown products. It is also reasonable to assume that laminin is a disordered synthetic product of RPE cells due to its close proximity to the basal cytoplasmic membrane.

LAMININ IN BRUCH'S MEMBRANE

The occurrence of laminin in deposits in the inner collagenous layer and between the outer collagenous layer and the basement membrane of the choriocapillaris appears to be unique to the aged macula. As these deposits were considerably more common in intercapillary spaces, they may represent remnants of retreating choriocapillaris. Alternatively the deposits may be the product of a senescent RPE. The latter theory is supported by embryonic studies which have shown that in the development of Bruch's membrane there is an extension outward one layer at a time from the basement membrane of the RPE.[34] Since the RPE has been shown in cell culture studies to produce all of the extracellular matrix components present in Bruch's membrane it is reasonable to assume that much, if not all, of Bruch's membrane is laid down by the RPE.[12] It is therefore conceivable that laminin deposits observed in our study within Bruch's membrane are the synthetic products of RPE cells and are not derived by diffusion from the choriocapillaris. It may be that such deposits are peculiar to aging and in being secreted in a monomeric form have polymerized within Bruch's membrane. On no occasion was an asssociation observed between laminin and the elastic tissue either in Bruch's membrane or in the supply vessels of the macular choroid.

In previous studies of aged human ciliary body and outflow system we noted plaques of extracellular matrix material in the tips of longitudinal ciliary muscle fibres[29] and in the cribriform layer.[26] These plaques bear a striking resemblance to the early forms of basal linear deposit seen in this study and in each location the extracellular matrix deposits were morphologically similar. The immunolabelling patterns for laminin and type IV collagen were also similar. It is interesting to speculate that since in all three regions the tissues act as a barrier to fluid drainage, metabolic byproducts may stimulate extracellular matrix deposition.

Finally, it is appropriate to consider the significance of the present study in relation to adhesion of the RPE to Bruch's membrane. The occurrence of discrete patches of laminin labelling between the inner collagenous layer and the RPE basement membrane could be attributed to the presence of anchoring plaques in a rudimentary basement membrane complex. We have observed a similar labelling pattern in the corneal epithelial basement membrane complex.[27] That the RPE is firmly adherent to its basement membrane is highlighted in the clinical condition of RPE detachment: here the site of cleavage occurs between the RPE basement membrane and the inner collagenous layer rather than between the RPE and its basement membrane.[35] This preferential adherence has been confirmed by scanning electron microscope studies of RPE exposed to trypsin digestion: the basement membrane separated from the inner collagenous layer rather than the RPE.[35] Firm adherence of the RPE to its basement membrane is presumably mediated by hemidesmosomes which have been described in the basal cell processes of the RPE.[36] This in turn would suggest the existence of a basement membrane complex with anchoring fibrils and anchoring plaques such as that seen in corneal epithelium.[37 38] In an immunoelectron microscope study of aged human cornea we were able to demonstrate the presence of laminin in the anchoring plaques of the basement membrane complex.[27] We would therefore suggest that labelling observed between the RPE basement complex and the inner collagenous zone may be due to the presence of anchoring plaques.

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Induced chorioretinal venous anastomosis in experimental retinal branch vein occlusion

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Abstract

Iatrogenic retinal vein to choroidal vein anastomoses were created using laser photocoagulation in six of seven dog eyes in which a partial branch retinal vein occlusion had previously been created photochemically. A similar attempt to create an anastomosis was made in six control eyes in which no branch vein occlusion was present. In the eyes in which a branch retinal vein had been created, a venous chorioretinal anastomosis appeared to be present by 3 to 6 weeks. In three control eyes similar venous anastomosis was created; however this took 6 to 8 weeks to develop and was of much smaller calibre than the one that developed in the presence of a partial branch retinal vein occlusion. No adverse complications were noted in the period of the study (3 months). This study demonstrates that chorioretinal venous anastomoses can be created and may be of use in the treatment of partial retinal vein occlusions that show signs of progression.

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Retinal venous occlusive disease is a common cause of visual loss in the elderly and in those with hypertensive and/or arteriosclerotic vascular disease. The occlusion is thought to be caused by an intraluminal venous thrombosis which produces a variable degree of obstruction to venous outflow.[1] Depending upon the degree of obstruction, the clinical features of a partial or complete occlusion are produced. In the complete form there is irreversible retinal ischaemia and severe visual loss occurs.[2,3] In the partial form, a variable degree of venous stasis occurs and the capillary vasculature remains largely intact. In this latter group, visual loss is often initially less severe,[2,3] and is usually caused by retinal oedema secondary to the incompetence of the capillary circulation owing to the raised intraluminal venous pressure.

Retinal venous occlusions may occur in either the central, a hemicentral, or a branch retinal vein. In each case in the initial stages, the only channel for the venous blood to exit the eye is blocked to a varying degree. In the later stages of the disease, some collateral circulation may develop, but often by this time the potential for full visual recovery has been lost due to irreversible changes in the macular region. These usually take the form of varying degrees of ischaemia, cystoid macular oedema, pigmentary dispersion, or preretinal fibrosis. In the cases of branch or hemicentral retinal vein occlusion, these collaterals may take the form of a vein to vein anastomosis to bypass the occluded segment with the venous blood then exiting the eye through the central retinal vein. In a central retinal vein occlusion, however, the only possibility of bypassing the obstruction would be the development of a venous anastomosis between the retinal and choroidal circulations. Such connections may occur at the disc as optociliary anastomosis, however these are slow to develop and do not form in all cases.

This study explores the possibility of creating an iatrogenic anastomosis between the retinal and choroidal venous circulations distal to the disc in an experimental model of a branch retinal vein occlusion. If collateral vessels such as these can be induced to occur between a high pressure circulation such as exists with an obstructed retinal vein and a low pressure circulation such as the choroidal venous system,[4] the prevention of a closed loop circulation and its ischaemic consequences may result.

Materials and methods

Branch retinal vein occlusions were created in one eye in nine mongrel dogs (7·0–20 kg) aged from 8 to 18 months. All experimental procedures were carried out under intravenous thiopentone and nembutal anaesthesia by controlled continuous intravenous infusion. Further ocular anaesthesia was obtained by topical 1% amethocaine eye drops and local subconjunctival injection of 1% lignocaine to ensure that the area to be grasped by fixating forceps was adequately desensitised. Pupils were dilated with phenylephrine hydrochloride (10%) and tropicamide (1%) eye drops for all procedures.

The branch retinal vein occlusion was created in the inferior retina of one eye in each dog away from the tapetal area. A focal thrombosis was induced photochemically in an inferior branch retinal vein using argon green laser light at 514 nm and intravenous rose bengal (50 mg/kg).[5,6] A small segment of the retinal vein, one disc diameter away from the disc, was irradiated with the argon laser via a contact lens using a power setting of 100–150 mW with a duration of 0·2 seconds and a spot size of 100 μm. This was performed while the rose bengal was either in full venous circulation or in a recirculation phase. Approximately 15 to 20 applications were required to stop the blood flow in the thrombosed vessel. Following this, engorgement of the distal vein was noted with the development of scattered intraretinal haemorrhages within its drainage area. Immediately after the occlusion was created, a high intensity small spot size laser burn (50 μm at 1·0 to 1·5 W and with a duration of 0·1 seconds) was placed over a small peripheral tributary vein in the drainage distribution of the occluded vein. The aim was to disrupt the

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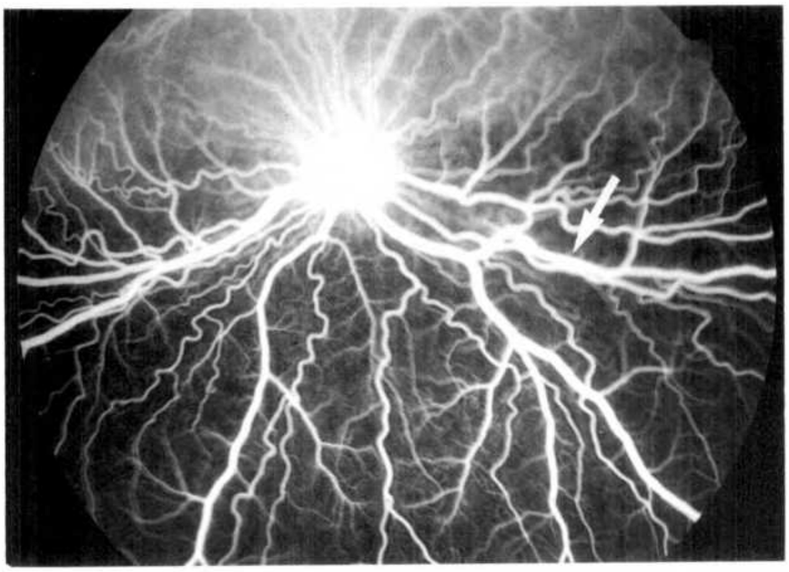

Fig 1A

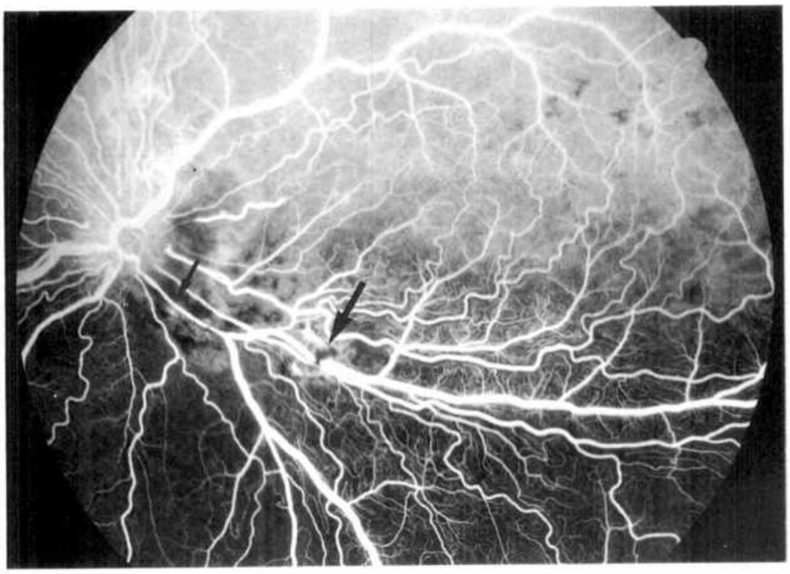

Fig 1B

Figure 1 (A) Fluorescein angiogram (full venous) taken before the creation of the branch retinal vein occlusion. The site where the anastomosis will be created is shown (arrow). (B) Fluorescein angiogram (full venous) taken 3 weeks after the creation of the vein occlusion. The area of the vein irradiated to create the occlusion is patent but narrow (small arrow). At the site of the high intensity laser burn (large arrow) a chorioretinal anastomosis may now be present as the distal portion of the vein appears to drain into the choroid.

vessel, the underlying retinal pigment epithelium, and Bruch's membrane, and to produce a small choroidal haemorrhage. In the other eye a similar small laser burn was placed over a small tributary vein in the distribution of an inferior branch retinal vein.

Early lysis of the thrombosis was prevented by the administration of tranexamic acid 25 mg/kg orally four times a day for 3 weeks. Fluorescein angiograms and fundus photographs using a fundus camera (60° Canon CF602A) were performed before the photothrombosis and at 1, 2, 4, 6, 8, and 12 weeks.

The animals were sacrificed by Lethobarb injection at the conclusion of the study. The eyes were immediately enucleated, bisected, and their posterior segments fixed in 2·5% glutaraldehyde in phosphate buffer and prepared for light and electron microscopic studies. Specimens of full thickness retina and choroid were then taken from the site of the high intensity laser burn where the developing chorioretinal anastomosis was present. The specimens were thereafter post fixed in osmium tetroxide, dehydrated, and embedded in epoxy resin. Serial sections, 2 μm thick, were taken and stained with toluidine blue for light microscopic studies. Ultrathin sections stained with uranyl acetate and lead citrate were used for electron microscopic studies.

A further animal was sacrificed 1 hour after a branch retinal vein occlusion was created photochemically. Specimens of full thickness retina and choroid were then taken from the region of the irradiated vein for histological study to confirm that an occlusion had been created.

Results

Partial retinal branch vein occlusions were created in seven of the nine eyes. In the remaining two eyes complete branch retinal vein occlusions were created which caused a localised serous retinal detachment. This serous detachment lasted only 1 to 2 weeks. However the retinochoroidal separation prevented a chorioretinal anastomosis developing at the site of the high intensity laser burn. In the seven eyes in which a partial branch retinal vein occlusion was created, a venous chorioretinal anastomosis occurred at the site of the high intensity laser burn in six eyes. By 3 to 6 weeks, fluorescein angiograms appeared to demonstrate blood flow from the retinal vein into the choroidal circulation at the site of the high intensity laser burn in all six eyes (Fig 1). The size of the venous chorioretinal anastomotic vessel increased progressively over the following weeks. Both the proximal and distal parts of the vein were seen to drain into the choroid. Retrograde flow was seen in the proximal vein with blood flowing away from the disc to the site of the anastomosis (Fig 2). Following the photothrombosis, the area of the retinal vein irradiated remained narrow but patent in the seven eyes with partial branch retinal vein occlusions. In the six eyes in which a chorioretinal anastomosis was successfully created, the proximal part of the vein progressively narrowed to the point of total occlusion over 2 to 3 months as the chorioretinal anastomosis developed. The area of total occlusion was usually just distal to the area irradiated with the laser.

In the fellow eyes, high intensity control laser burns were placed in six eyes over a similar small venous tributary in the drainage distribution of an inferior branch retinal vein. In three (50%), a chorioretinal venous shunt was created. Definite fluorescein angiographic evidence demonstrating flow into the choroid was seen at 6 to 8 weeks in all three eyes. The size of the anastomotic vessel was smaller compared with the eyes in which a branch retinal vein was first created. Some narrowing of the proximal portion of the vein was seen as the anastomotic vessel developed; however this did not progress to the stage of complete closure.

Histological examination of the eye enucleated

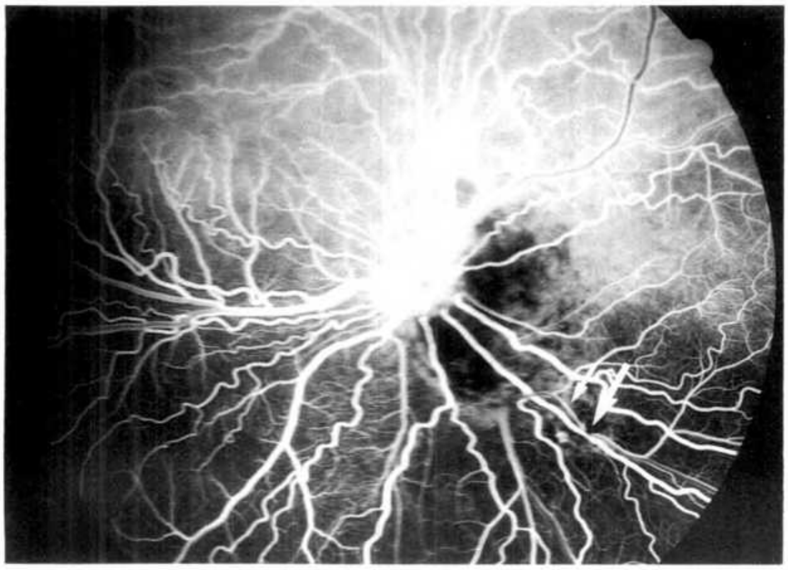

Fig 2A

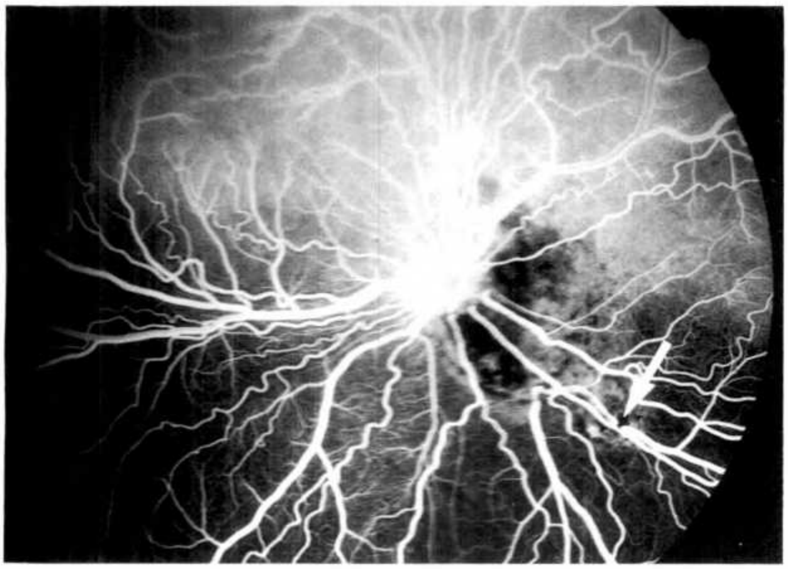

Fig 2B

Figure 2 Fluorescein angiograms early venous (A) and late venous (B) taken at 12 weeks. Definite laminar flow is now seen in (A) with retrograde venous flow (small arrow) away from the disc to the site of the chorioretinal anastomosis (large arrow). Both the proximal and distal portions of the vein now drain into the choroid with no connection to the disc. The segment of vein next to the disc where the photothrombus was originally created has now completely closed.

1 hour after photothrombosis of a retinal vein confirmed that a total occlusion was present at that time (Fig 3). Clinically in the other eyes in the series that were allowed to progress, the vein appeared to have partially reopened by 1 to 2 days and this was confirmed by the fluorescein angiogram that was performed at 1 week. Despite the use of rose bengal as a photothrombotic agent and lower laser energy powers, histological examination showed destruction and necrosis in the surrounding retina and severe damage to the vessel wall as well as an intraluminal thrombus (Figs 3 and 4).

At the conclusion of the study (3–4 months) the eyes were enucleated and the area of the high intensity laser beam was examined histologically. In the six eyes in which blood flow from a retinal vein into the choroid was demonstrable by fluorescein angiography an anastomotic vessel was detected by serial sections taken at 2 μm intervals. This vessel connected a retinal vein to a choroidal vein and was usually of large calibre (100 μm) (Fig 5). Surrounding the chorioretinal anastomotic vessel was a dense full thickness chorioretinal scar composed of proliferated retinal pigment cells, gliotic tissue and pigment laden macrophages. Significant persistent subretinal or retinovitreal neovascularisation in the area surrounding this scar was not seen in this study.

Discussion

The current therapeutic options for the treatment of retinal venous occlusions are limited in their effectiveness and are mainly non-specific in that they fail to address the basic pathological process causing the obstruction in the retinal vein. In the case of a branch vein occlusion the obstruction lies in the vein, usually at a point where it is crossed over by an artery.[7,8] In a hemicentral vein occlusion the obstruction lies in one of the dual retinal venous trunks as it exits the optic disc. Finally, in the case of a central retinal vein occlusion the obstruction lies in the central retinal vein in the region of the laminar cribrosa.[1] In each case the obstruction is owing to an intraluminal thrombus plus secondary factors such as endothelial cell proliferation. This obstruction blocks venous outflow to a variable degree, producing either a complete or partial obstruction. Where a complete obstruction has occurred there exists in the affected area of the retina a closed loop circulation with consequent ischaemia, capillary loss, and cell death. In this form there is little or no prospect for improvement of function in the affected area once eventual recanalisation occurs. Treatment for complete occlusions consists of laser photocoagulation of the ischaemic area with the aim of preventing neovascular complications rather than the restoration of vision.[9] In the partial retinal vein occlusions venous outflow is not completely blocked and in the initial stages there is usually little or no ischaemia and capillary loss. This does change with time as the intraluminal thrombus causing the obstruction may propagate, increasing the level of obstruction, or undergo recanalisation. In partial venous occlusions therefore there is often a period of time available where it would be possible to intervene and reduce the level of obstruction should such a therapeutic option exist.

In the case of the central retinal vein occlusions the partial form is the more common (54–78%).[10,11] In this group 40% will have resolution of the occlusion and a return of near normal vision. A further 40% will eventually develop normalisation of retinal circulation but will be left with chronic macular oedema and impairment of vision. The remaining 20% will progress to the complete form.[12] In those that do progress from the incomplete to the complete form, the time of transition may vary from 1·5–26 months with a median of 4·5 months.[11] Serial parameters such as funduscopy, fluorescein transit times, estimation of central retinal venous pressure by ophthalmodynometry, and electroretinography

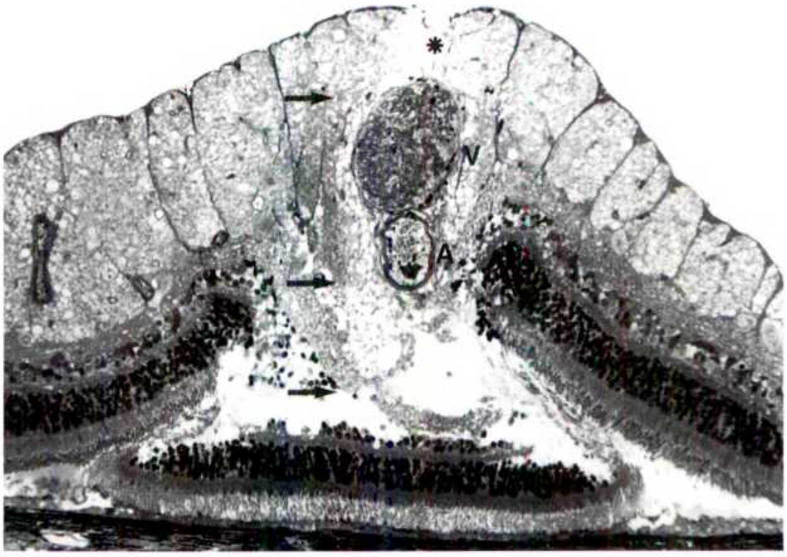

Figure 3 Light photomicrograph of a retinal vein (V) and an artery (A) with occluded lumens 1 hour after irradiation with argon green laser in the presence of rose bengal in the inferior retina away from the tapetal area. Retinal structure is significantly disorganised. Intense necrosis of all retinal layers (arrows) including the internal limiting membrane (*) were observed (toluidine blue, magnification ×130).

can be used to detect changes in the level of obstruction. In those partial retinal vein occlusions that show signs of increasing levels of obstruction over a period of time, or in those who have persistently high levels of retinal venous pressure and macular oedema, therapeutic options should be considered. Unfortunately at this time there is no means of treatment that is safe and will prevent the possible progression of a partial central retinal vein occlusion to the complete form.

Numerous therapeutic approaches have been tried in the treatment of central retinal venous occlusion, most with little or no success. Therapies such as *x* rays,[13] topical pilocarpine, cholesterol lowering agents,[14] and vitamins[15] have been used in the past. These have no scientific basis and not surprisingly were ineffective. Ocular hypotensive agents may improve retinal blood flow by lowering venous resistance but offer no sustained benefit. Anticoagulants have also not proved effective.[15] As thrombus organisation and endothelial cell proliferation may occur quite early their potential benefits would seem to be limited.[1] Corticosteroids[16] may help to reduce macular oedema in the short term by reducing endothelial cell permeability but as there is no direct evidence that a vasculitis of the central retinal vein is the primary cause of the occlusion it would appear that they also offer no long term benefits. Indeed, Green *et al*[1] have demonstrated that the chronic inflammatory infiltrate found in the region of the thrombosis in the central retinal vein is a result of the occlusion rather than the cause.

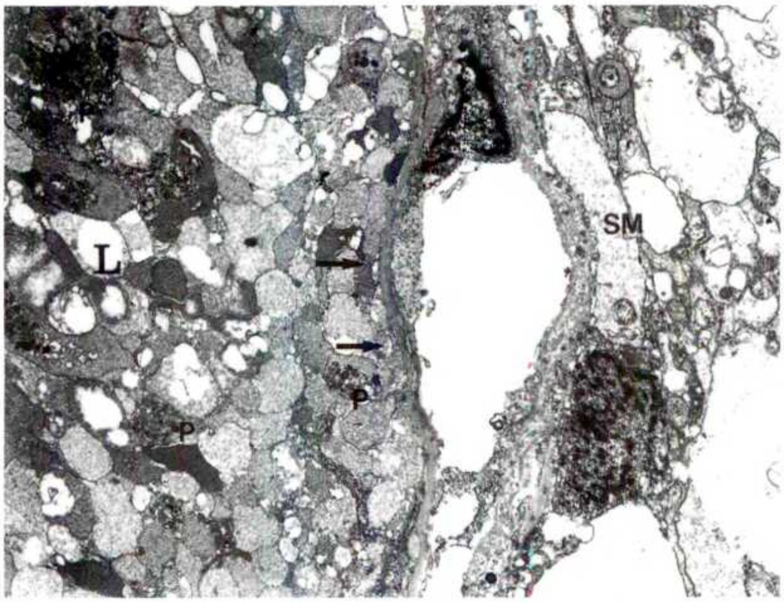

Figure 4 Electron micrograph of the vein seen in Figure 3. The lumen of the vessel (L) is filled with finely granular platelet material (P). The endothelial cellular lining is no longer recognisable, and the basement membrane (arrow) is focally exposed. The smooth muscular cells (SM) are severely damaged, with disruption of their cell membranes and cytoplasmic organelles (magnification ×3950).

Thrombolytic agents such as streptokinase[17] have been associated with an unacceptable incidence of severe side effects and are no longer used. New agents such as tissue plasminogen activators,[18] which are clot selective and do not have an effect on circulating plasminogen, offer a theoretical advantage but the results of clinical trials remain to be seen. Isovolaemic haemodilution[19] has been shown to improve visual acuity in a study on non-ischaemic central retinal venous occlusion. The improvement is probably due to reduced blood viscosity allowing improved retinal microcirculation. There is no effect, however, on the degree of obstruction to venous outflow.

None of these forms of treatment are currently widely used either due to a lack of effectivity or deleterious side effects. Central retinal venous occlusion is thought in most cases to be caused by compression of the vein in the region of the lamina cribrosa by a thickened and more rigid arterial wall as a result of systemic hypertension and/or arteriosclerosis. This leads to turbulence causing endothelial damage in the retrolaminar portion of the vein and subsequent platelet aggregation and thrombosis.[1,20] Endothelial cell proliferation and organisation of the thrombus then occurs and later recanalisation may develop,[1] but by this time irreversible visual loss may have occurred. There is outflow obstruction in central retinal venous occlusion and the only therapeutic modalities mentioned above which have shown some degree of success either try to lyse the thrombus or, by reducing viscosity, enable the blood to exit through a partially occluded lumen. Even though theoretically these might help in the short term, the initial predisposing factors remain in the region of the lamina cribrosa. The patient is therefore placed at continued risk of either a new thrombus developing which may progress to a complete occlusion and/or the risks of systemic complications of the treatment – for example, fibrinolytics.[17] Recurrent thrombosis has been confirmed histologically in a large series where in some eyes the formation of a fresh thrombus immediately posterior to an older recanalised fibrotic thrombus was noted.[1]

In order to be effective, the form of treatment

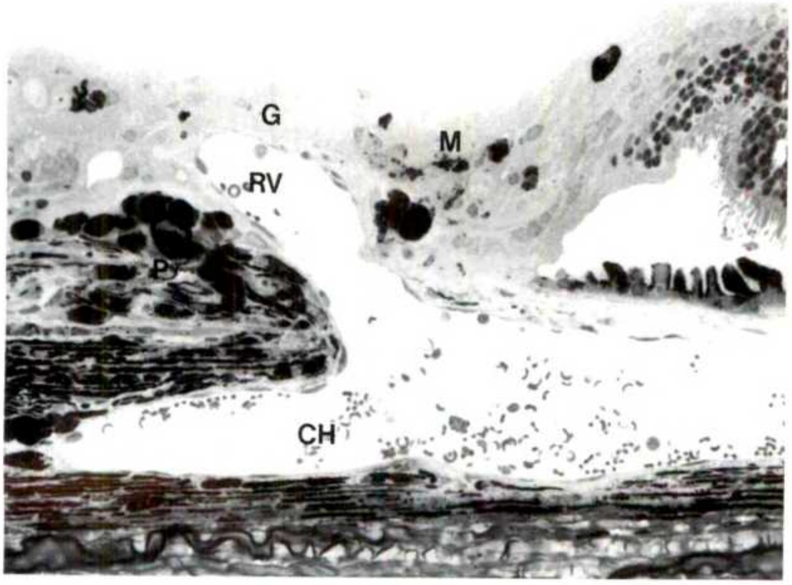

Figure 5 Light photomicrographs showing a large choroidal vein (CH) with an anastomosis to a retinal vein (RV). The anastomotic vessel is surrounded by gliotic tissue (G), proliferated retinal pigment epithelial cells (P), and pigment laden macrophages (M). The venous shunt is of large calibre (approximately 100 μm) and connects to a similarly large choroidal vein (toluidine blue, magnification ×270).

to be used must permanently improve the retinal circulation and the currently available ones fail to do this. Alternative pathways for venous blood to exit the eye may have to be considered rather than concentrating on ways to force it through what is probably a permanently damaged central retinal vein. Such pathways may occur at the disc as optociliary anastomoses in vein occlusions; however these do not occur in all patients and may take considerable time to develop. Other such connections between the retinal and choroidal circulation may occur away from the disc and have been reported in association with inflammatory chorioretinal scars,[21-24] age-related macular degeneration associated with subretinal neovascularisation,[25-27] penetrating trauma,[28] choroidal rupture,[29] and meridional folds at the ora serrata.[30] Chorioretinal anastomoses have also been induced experimentally with laser photocoagulation.[31] This study by Wolf and Goldberg explored the possibility of reperfusing experimentally occluded retinal arterioles using intense photocoagulation to create a chorioretinal arterial anastomosis. They were successful in nine out of 19 sites with the time required for the establishment of the anastomosis ranging from 7 weeks to 9 months. In our study an attempt was specifically made to create a retinal vein to choroidal vein anastomosis. This was done by first creating a partial venous occlusion thus raising the intraluminal pressure to encourage the passage of blood into the lower pressure choroidal venous circulation. The site of the anastomosis was placed in the mid-periphery away from the posterior ciliary arteries and larger choroidal arteries to lessen the likelihood of a choroidal artery to retinal vein connection. In the seven eyes in which a partial branch retinal vein occlusion was created a venous chorioretinal anastomosis was successfully induced in six eyes. Evidence of blood flow from the retinal venous circulation into the choroid was demonstrable by 3 to 6 weeks in all eyes by fluorescein angiography. As discussed earlier, most partial central retinal vein occlusions that progress to the complete form do so over a period of 1·5 to 4·5 months.[11] In this series a retinochoroidal venous anastomosis was induced and appeared to be functioning 3 to 6 weeks after a partial branch retinal vein occlusion was created. This is before most partial central retinal vein occlusions observed clinically progress to the complete form and this technique may therefore be useful in the management of such occlusions which show signs of increasing outflow obstruction. Even though in this series the anastomosis was created in a partial branch retinal vein occlusion, the establishment of a retinochoroidal venous anastomosis, distal to the site of the thrombosis in other forms of retinal vein occlusions, should relieve the outflow obstruction and allow the retinal venous pressure to return to normal. The site of the obstruction in a central retinal vein occlusion lies at the level of the lamina cribrosa proximal to the anastomosis of the superior and inferior venous circulation on the optic disc. This would allow the passage of venous blood from one hemisphere into the other and out through the chorioretinal anastomosis.

In this series the creation of a partial branch retinal vein occlusion before the attempt to create a chorioretinal venous anastomosis appeared to increase the likelihood of a successful anastomosis occurring. Venous chorioretinal anastomoses were created in six out of seven eyes in which a partial branch retinal vein occlusion was created first, and in only three out of six control eyes. In addition, the anastomosis developed at an earlier stage in the experimental eyes and appeared to carry a higher volume of blood. This is illustrated by the fact that in the eyes with the partial branch retinal vein occlusion the proximal part of the vein narrowed to the point of total occlusion over 2 to 3 months. This narrowed segment included the segment treated with laser to create the initial photothrombosis and a portion of the vein distal to it, and was presumably caused by a progressive vascular steal as a chorioretinal anastomosis developed and the pressure differential between the retinal and choroidal veins lessened. In the control eyes, over the same period, some narrowing of the proximal vein was seen but this did not progress to the stage of complete closure. The prior establishment of a partial branch retinal vein occlusion thus raising the intraluminal venous pressure in one group appears to increase both the likelihood and the speed of development of a venous chorioretinal anastomosis in response to a high intensity laser burn over one of the tributary veins.

In this animal model a reproducible venous chorioretinal anastomosis could be created and no significant complications from the high intensity laser burn were seen. To create the shunt the laser energy has to be sufficiently intense to disrupt Bruch's membrane, allowing vessels from the choroid to anastomose with the disrupted venous tributary. The higher pressure in the obstructed vein should then encourage the formation of a larger anastomotic vessel into the choroid. Although not seen in this small series, the potentially serious complications of choroidal neovascularisation arising through the laser-created defect in Bruch's membrane could occur. Serous or haemorrhagic detachments of the retinal pigment epithelium, sensory retina, or both could occur as well as progressive exudation, inflammation, and organisation leading to a subretinal cicatrix. Subretinal neovascularisation leading to large vascular complexes and scarring involving the retina and even extending into the vitreous have been reported after experimental disruption of Bruch's membrane with laser photocoagulation.[32 33] Significant subretinal neovascularisation around the site of the high intensity laser burn was not seen in our series. Perhaps the rapid establishment of a larger channel may have caused regression of the remaining neovascular fronds growing through the defect in Bruch's membrane by shunting blood away from them.

In conclusion, the establishment of a retinochoroidal venous anastomosis distal to the site of the thrombosis in retinal venous occlusions should relieve the outflow obstruction and allow the retinal venous pressure to return to normal. If this can be created in a partial retinal vein occlusion prior to its transition to the complete form, the potential for some return of visual function remains. Further long term studies are being conducted to evaluate fully the effect of the retinal vein to choroidal vein anastomosis on the evolution of retinal vein occlusions and to monitor the possible development of complications.

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AgNOR counts in conjunctival malignant melanoma lack prognostic value

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Abstract

Using a silver staining technique, argyrophilic nucleolar organiser region-associated proteins (AgNORs) have been studied in routinely processed paraffin sections of 46 invasive malignant melanomas (MM) of the conjunctiva. The aim of this retrospective study was to assess the value of the AgNOR method as a prognostic indicator for this neoplasm. The 46 cases were divided into two groups: (A) 14 cases of MM that metastasised and caused death of the patient within 5 years of (histological) diagnosis, and (B) 32 cases of MM that did not metastasise and in which patients survived beyond 5 years. The mean of the AgNOR counts per nucleus was 7·03 (95% CI: 5·81–8·24) in group A, and 7·15 (95% CI: 6·53–7·77) in group B. A comparison using a multifactor analysis of variance (ANOVA) model, which corrected for possible confounding effect of tumour thickness, site, and cell type showed no significant difference in AgNOR counts between groups A and B ($p=0·8$). Analysis by the Cox proportional hazards regression model showed that survival was not influenced significantly by the mean AgNOR number (hazard ratio: 0·92). Whereas the AgNOR technique may be used to distinguish benign from malignant melanocytic lesions of the conjunctiva, we conclude it has no value in predicting the outcome for patients with conjunctival MM.

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Nucleolar organiser regions (NORs) are loops of ribosomal DNA which transcribe to ribosomal RNA. NORs are associated with the five acrocentric chromosomes (13, 14, 15, 21, and 22) and can be visualised in the nuclei of cells as black/brown dots by virtue of the argyrophilia (Ag) of their associated proteins, including RNA polymerase-1, B-23, and C-23.[1]

Silver staining of the AgNOR proteins has been used as a technique to study the nucleolar morphology and the variations of nucleolar activity,[2] and the number and size of AgNORs are thought to reflect rDNA transcriptional activity.[3] Since the introduction of the one step, simplified AgNOR technique,[4] which can be applied to routinely processed paraffin wax embedded histological specimens, several studies[5–11] have been conducted to evaluate the possible association between AgNORs and malignancy of melanocytic lesions. The AgNOR technique has been applied to melanocytic tumours of the skin,[5,6,7] and those of the eye, including the iris,[8] choroid,[8,9,10] and conjunctiva.[11]

These studies indicated that enumeration of AgNORs is useful in discriminating benign from malignant lesions, though some overlap in AgNOR counts was observed. There have been only few reports[9,10,12] that studied the prognostic value of the silver staining method in melanocytic lesions. The aim of this study was to investigate the prognostic significance of AgNOR counts in malignant melanoma of the conjunctiva.

Materials and methods

SELECTION OF CASES

Clinical information on patients with conjunctival malignant melanoma who were treated in the ocular oncology unit of Moorfields Eye Hospital and St Bartholomew's Hospital was retrieved from a database (Paradox 3), maintained at the Institute of Ophthalmology. Slides containing the histological sections of the tissue biopsy specimens of these patients were reviewed to verify the diagnosis of invasive malignant melanoma (MM) of the conjunctiva.

We selected 60 cases that had been followed up for 5 or more years or to the date of death owing to conjunctival melanoma. Patients who died within 5 years from any cause other than metastatic melanoma were not included. For each case the location, the maximum thickness, and the cell type of the surgically (completely) excised original tumour were recorded. After the silver staining of the 60 histological sections, 14 cases were discarded because of difficulties in visualisation of AgNORs, mainly caused by heavy melanin deposits obscuring the view or poor staining.

The 46 remaining cases were divided into two groups for comparison of AgNOR counts: (A) 14 cases of MM in which death from metastasis occurred within 5 years of diagnosis, and (B) 32 cases of MM that did not metastasise, with patients' survival beyond 5 years.

SILVER STAINING TECHNIQUE

Sections were cut at 3 μm thickness and were dewaxed in xylene and hydrated through graded ethanols. The sections were processed to demonstrate AgNORs at room temperature for 30 minutes.[13] The reaction mixture comprised 2% gelatin in 1% aqueous formic acid. This was mixed in a proportion of 1:2 volumes with 50% aqueous silver nitrate under dark room conditions. After staining the sections were exposed to xylene and mounted in synthetic medium.

COUNTING PROCEDURE

All sections were examined by two observers, using an oil immersion lens (×100). Both observers recorded the total number of AgNORs

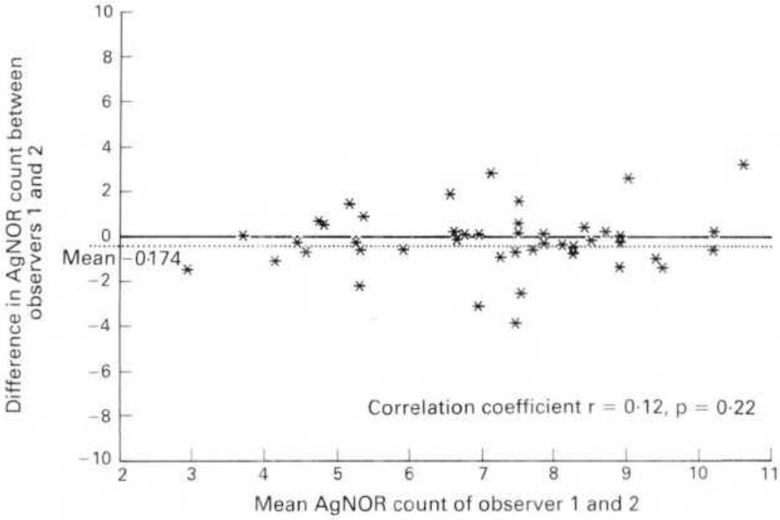

Figure 1 Difference between observer 1 and 2 in AgNOR count of the same specimen (C1-C2), plotted against the mean of the two counts (C1+C2)/2. The differences are mostly trivial, with a small mean of −0·174, and appear to be independent of the mean count, showing no systematic pattern of change in magnitude with higher values of the mean count. The correlation of the differences with the mean values is small and not significant, so that an assumption of independence is not contradicted by the data.

per nucleus, including both nucleolar and extranucleolar NORs, for 30 nuclei, as suggested by Orrell *et al*,[7] and calculated a mean value. Subsequently, a mean value of both observations (total of 60 nuclei) was calculated for every section.

STATISTICAL ANALYSIS

The mean AgNOR counts in the two groups were compared using a multifactor analysis of variance (ANOVA) model. This allowed adjustments to be made for possible confounding effect of three other variables: tumour thickness, cell type, and site. Further analysis, to evaluate the relationship between AgNOR counts and survival, was carried out using the Cox proportional hazards models.

The agreement between the two observers in evaluating the mean count of AgNORs was assessed by analysis of the difference in the paired observations. The mean difference was computed to give a measure of bias, and the standard deviation of the differences provided a measure of error owing to – for example, poor repeatability. The hypothesis of zero bias was tested by a paired *t* test.[14] A plot of the differences between the two observers against the mean of the two observers (Fig 1) was constructed to demonstrate the magnitude of disagreement in the AgNOR counts by the two observers, and to show dependence or otherwise of the degree of agreement upon the magnitude of the counts. The presence or absence of such dependence was formally tested though correlation analysis. A similar analysis was done for nine pairs of repeat counts by one of the observers.

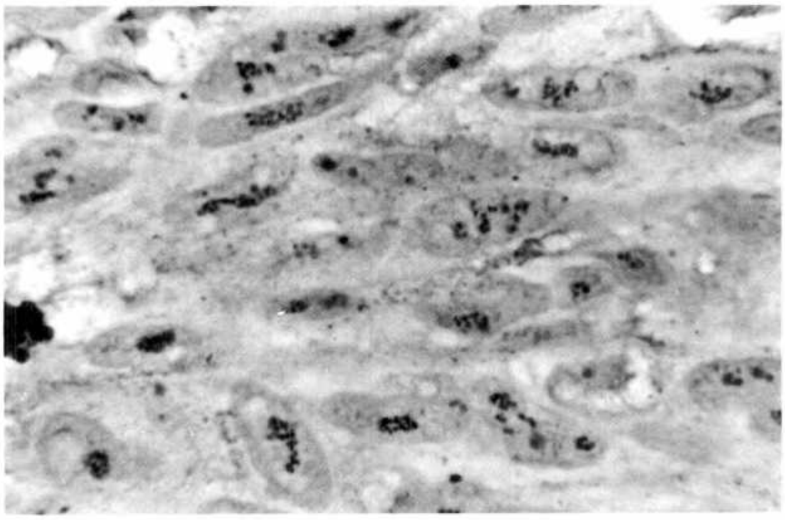

Figure 2 Conjunctival malignant melanoma: high number of AgNORs, visible as black dots in the nuclei of the tumour cells (silver stain, ×280).

Results

In the selection of specimens AgNORs were visible as black dots of varying sizes in the nuclei (Fig 2). In the majority of cases the dots were clustered within an argyrophilic nucleolus, but in some cases AgNORs were dispersed throughout the nucleus. In the 3 μm sections there appeared to be little overlap of cells, which might give rise to artificially high counts in thicker sections.

Data from the AgNOR counting are shown in Table 1. The mean AgNOR counts were 7·03 (range 2·95–10·6) in group A, and 7·15 (range 3·7–10·2) in group B. The difference was not significant (p=0·8), and remained so after adjustment for possible confounding effect of tumour thickness, cell type, and site (Table 1). No adjustment was necessary for the influence of multifocality of melanoma at diagnosis as a simular incidence of multifocal lesions was seen in both groups.

Analysis by the Cox proportional hazards regression model incorporating the three possible confounders showed that survival was not influenced significantly by the AgNOR counts. The hazard ratio for the mean AgNOR count term was close to unity (0·92) with a 95% confidence interval of 0·72–1·16 (p=0·46). There were no significant higher order interactions, indicating no effective modification by any of the other three factors – that is, the lack of association between AgNOR count and survival was consistent in subgroups with different tumour thickness, cell type, or tumour site.

There was good agreement between the two observers in counting AgNORs. The mean of the differences between the paired counts was −0·174 (standard error=0·2, p=0·4), indicating no significant bias. The standard deviation of the differences was 1·36. The differences (degree of disagreement) did not seem to depend upon the magnitude of the counts (Fig 1). The assumption of independence was not contradicted by the data (correlation coefficient r=0·12, p=0·22). The intraobserver agreement, in repeat counts of a small subsample of nine specimens, also showed close agreement (mean of differences= 0·3, standard deviation=0·52).

Discussion

Malignant melanoma of the conjunctiva is rare but is among the most serious of ocular

Table 1 Analysis of variance comparing the mean AgNOR count in the two groups A and B (those who died within 5 years of follow up and the survivors respectively)

Group	*No*	*Mean AgNOR count*	*Standard deviation*	*Standard error*	*95% confidence interval*	
A	14	7·03	2·10	0·56	5·81	8·24
B	32	7·15	1·72	0·30	6·53	7·77
Total	46	7·11	1·82	0·27	6·57	7·65

F statistic = 0·043; p value = 0·8

After adjusting for effects of thickness, cell type and site:

F statistic = 0·016; p value = 0·9

Cochran's C and Bartlett-Box F tests: p values are 0·36 and 0·39, indicating no violation of the 'homogeneity of variance' assumption

malignancies. This tumour may arise de novo, from a pre-existing naevus, or from an area of primary acquired melanosis (PAM). The latter precursor is acquired at adult age and is often multifocal, thus putting the patient at risk of multicentric melanoma. Silvers *et al*[15] have demonstrated that thickness of the patient's thickest conjunctival melanoma is a good indicator of poor prognosis, a finding which was confirmed by Folberg *et al.*[16] Other factors that may be prognostic indicators include tumour location and cell type. Several authors have found a worsened outcome in multicentric melanoma and in melanomas involving the fornices, the palpebral conjunctiva, and the caruncle,[17 18 19] but there has been no large study which has demonstrated a higher death rate from melanomas arising from PAM with atypia.[16 17]

The number of AgNORs has been reported to be of prognostic value in breast carcinomas.[20 21] In a study of uveal melanomas, Marcus *et al*[10] found a correlation between AgNORs and the 5 and 10-year estimated survival. They concluded that AgNORs may therefore be of value in predicting prognosis for uveal melanomas, but their data remain to be correlated to survival statistics. In a previous study from this group[9] we have not found this to be true and this non-agreement is echoed in cutaneous MM where Howat *et al*[12] also found no correlation between AgNOR counts and metastasis. In the latter study it was argued that while AgNORs may reflect cell proliferation rate the development of metastases may be determined by a variety of other factors.

Our study showed no significant difference in mean AgNOR counts between the two comparison groups A and B, which represent cases with good and poor 5-year outcomes respectively. Had there been a true difference of at least 2·0 (for example, population mean of A=9 and of B=7), the study would have had a 95% probability of detecting it as significant (critical p value being 0·05). This suggests that the clinical outcome depends on factors other than AgNOR number.

The mean of the mean AgNOR counts in this study was 7·1, which is markedly higher than the mean count of 5·7 that was recently observed in another study of 14 conjunctival melanomas[11]; however, interestingly, they reported that none of their cases had a lower AgNOR count than 4·0, whereas in two of our cases we counted 3·7 and 3·0 AgNORs respectively.

Despite subjectivity in resolving single AgNORs within nucleolar argyrophilic clumps and the relatively small sample sizes, there was good inter and intraobserver agreement. Some of the apparent disagreement may be attributed to sampling errors. Whereas the AgNOR technique may be useful as a tool for the differential diagnosis of conjunctival or other ocular melanocytic lesions,[8-11] we conclude that assessment of AgNOR number is of no prognostic significance for MM of the conjunctiva.

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MINI REVIEW

Laser trabeculoplasty

Early attempts at laser treatment of open angle glaucoma met with limited success. Goniopuncture using the Q-switched ruby laser[1] caused a temporary reduction only of intraocular pressure (IOP), and argon laser photocoagulation of the trabecular meshwork, though producing sustained IOP reductions in some patients,[2] was accompanied by acute post-treatment rises in others. In 1979 Wise and Witter reported the successful reduction of IOP with few complications using the argon laser at lower energy levels than before.[3] They treated the full circumference of the trabecular meshwork applying 100 evenly spaced burns of 50 μm spot size at a power of 1000 to 1500 mW for 0·1 seconds and achieved an average fall in IOP of 10·3 mm Hg at 3 months in 41 patients. This success was subsequently confirmed by others and the technique employed today is substantially the same.

Pathophysiology

Wise and Witter postulated that the fall in IOP was a mechanical effect, the evenly spaced microscars reducing the diameter of the inner trabecular ring and reversing collapse of the meshwork with restoration of normal outflow function. That argon laser trabeculoplasty (ALT) acts by increasing the facility of outflow has been confirmed by tonographic[4] and fluorophotometric[5] studies but this mechanical theory, though attractive, has not been supported by animal or enucleated human eye tissue studies. It has also been observed that heat induced shrinkage of the trabecular collagen is a rapid process whereas the time course of the ALT response is relatively slow.[6]

From early histological studies it was clear that successful argon laser treatment was not dependent on the formation of a direct communication between the anterior chamber and Schlemm's canal. Ultrastructural changes seen in trabeculectomy specimens from patients previously treated by ALT include intratrabecular debris, distortion of trabecular beams and death of trabecular endothelial cells, leaving the damaged beams denuded. But there is also evidence of activation and migration of surviving trabecular endothelial cells to the burn site.[7] In many specimens cellular sheets extending from Schwalbe's line and covering the surface of the anterior meshwork have been observed. These sheets have been considered to represent an excessive repair response which contributes to failure of the laser treatment.

Increased trabecular cell division following ALT at sites distant to the laser burns has also been demonstrated in vitro using organ cultured trabecular meshworks, the majority of the cells originating in the anterior meshwork close to Schwalbe's line.[6] Two weeks after laser treatment these active cells are concentrated around the burn sites and it has been suggested that they may exert an influence on outflow resistance by causing alterations in the synthesis of the proteoglycan components of the extracellular matrix.[8]

ALT causes a temporary disruption of the blood ocular barrier resulting in aqueous protein flare and there is evidence that this is mediated by prostaglandins which can be synthesised by the trabecular meshwork. Post-ALT flare is maximal at 48 hours and there is a positive correlation at this time between the level of inflammation and IOP decrease which can be partially blocked by prostaglandin synthesis inhibitors. Of particular interest is the finding of Mermoud *et al*[9] that this correlation persists long after the inflammatory reaction has subsided and they considered the possibility that prostaglandin production might persist at a level sufficient to lower the IOP but too low to disrupt the blood ocular barrier.

Technique

The main treatment variables are the proportion of the angle treated, the size and placement of individual burns, and the energy used. Surprisingly, wavelength appears to be of little importance. No difference between the effect of argon blue-green and argon green lasers has been found[10] and the krypton laser,[11] the diode laser,[12] and others have all produced results comparable with those of argon.

Treatment of 180 degrees with 50 burns has been found by some investigators[13 14] to be as effective as full 360 degree treatment while producing significantly lower post-treatment IOP rises. Others have achieved greater effect with 360 degree treatment[15] but this can be more safely carried out in two treatment sessions of 180 degrees each.

The degree of IOP reduction is similar whether burns are placed on the anterior or posterior meshwork[16] but acute IOP elevation[17] and peripheral anterior synechiae (PAS) formation are more frequent with posterior placement. The accuracy of placement is facilitated by a small spot size and 50 μm has been almost universally used but Sherwood *et al*[18] using 150 μm and 350 μm spots obtained good pressure reduction though the larger spot was difficult to focus.

The effectiveness of ALT is independent of the duration of the burn if the total energy delivered is kept constant. With a duration of 0·1 seconds the effective power range lies between 500 mW and 1000 mW, lower than that originally used by Wise and Witter. Most authorities advocate adjusting the power level to obtain the minimum visible response of blanching of the meshwork and/or gas bubble formation.

Complications

The most serious complication of ALT is post-treatment acute elevation of IOP resulting in loss of vision. Some increase in IOP is very common and in one study a rise of more than 5 mm Hg occurred in 34% and of more than 10 mm Hg in 12% of patients who had undergone 180 degree ALT.[19] The frequency and severity of IOP elevations are increased by the use of higher energy levels, 360 degree treatment, posterior placement of burns, angle pigmentation, and a low preoperative facility of outflow.[20] Most post-treatment IOP peaks occur within the first 2 hours[21] but occasionally rises may be delayed and monitoring of IOP for 4 hours has been recommended. The cause of this IOP rise is uncertain but may result from swelling of the trabecular meshwork or obstruction of the trabecular spaces by debris. It is not prevented by steroids or antiprostaglandins but aqueous suppressants and miotics are effective as is apraclonidine, an α 2 agonist, which has been found[22] to reduce the incidence of all pressure rises by nearly two thirds and to eliminate all increases greater than 10 mm Hg.

PAS develop in a high percentage of patients undergoing ALT but these appear to be of little clinical significance and are not associated with a reduced IOP response. They develop more frequently with posteriorly placed burns[23] and with higher power levels.[24]

Other complications are relatively minor. Corneal endothelial damage has been reported[25] but prospective studies have failed to show any evidence of morphological or functional damage[26] and epithelial burns caused by errors of focusing are transient. Similarly uveitis is usually mild and transient but post-treatment topical steroids are often prescribed routinely.

Results of treatment

ALT significantly reduces IOP in the short term. In one large study a reduction of 6·4 mm Hg (26%) was found at 5 months in 237 patients with primary open angle glaucoma (POAG) on maximum medical treatment.[4] A greater reduction was obtained using ALT as the primary treatment with a fall of 9·0 mm Hg (33%) at 3 months in 264 patients with POAG.[27] Several studies have also shown a beneficial effect of ALT on the diurnal pressure curve with marked reductions of intraindividual IOP fluctuation in successfully treated patients.[28 29]

From the outset it was recognised that there was some loss of effect of ALT with time. By the mid 1980s it was evident that this loss was considerable. Schwartz *et al* found that their success rate of 77% at 2 years had fallen to 46% at 5 years[30] and Spaeth and Baez have reported that only one third of their patients with POAG could be considered successfully treated by ALT after 5 years.[31] Overall failure is highest in the first year and subsequently occurs at a rate approaching 10% per year. Retreatment of failed eyes that have undergone 360 degree ALT is significantly less successful than with initial treatment and loss of effect is more rapid. Richter *et al* retreated eyes that had undergone 180 degree ALT and achieved an IOP reduction of more than 3 mm Hg in only one third of eyes.[32]

The success of ALT is influenced by patient selection. Patients under 50 years of age respond less well but there is no difference between the sexes.[33] Black patients initially do as well as white patients[34] but loss of effect is more rapid with only half as many black patients considered successful after 5 years.[30] Survival curve analysis has shown the median time to an IOP of 21 mm Hg to be 12 months for black patients and 60 months for whites.

The average initial fall in IOP of eyes with POAG is about 30%. The response is more or less linear with the pretreatment pressure and, as might be expected, eyes with normal tension glaucoma show a smaller effect. The results of ALT in pigmentary glaucoma are conflicting with some evidence that older patients do less well,[35] but overall the response is similar to that of POAG. The largest pressure reductions are seen in eyes with exfoliative glaucoma but there is some evidence that failure occurs earlier than in eyes with POAG[36] and the pressure rise may be quite rapid. Other forms of secondary open angle glaucoma generally respond less well with uveitic and developmental glaucomas often showing little or no useful fall in IOP.

The role of ALT in the management of open angle glaucoma

Laser trabeculoplasty is an outpatient procedure that is well tolerated and relatively safe. It avoids the inconvenience and side effects of medical treatment and the risks of major intraocular surgery. But it also has drawbacks, the greatest of which is the loss of effect with time. Concern has also been raised about the possible adverse effect of ALT on subsequent drainage surgery. The incidence of encapsulated blebs has been found to be up to three times higher in eyes previously treated with ALT.[37]

For a number of years ALT was considered to be a logical next step in the management of open angle glaucoma when maximum tolerable medical treatment had failed to keep the IOP within 'normal' limits or prevent further field loss. ALT was regarded as successful for as long as surgery was delayed and in many studies this has been the criterion of success. More recently the role of ALT as a primary treatment in the management of POAG has been investigated and compared in a number of studies with both medical and surgical treatment.

Prospective trials comparing ALT with medical treatment have given results which appear to favour laser treatment but which must be interpreted with caution. The use of stepped medical regimens and the addition of medications to the treatment of uncontrolled 'laser first' patients makes longer term comparison of the two modalities difficult if not impossible. The Glaucoma Laser Trial Research Group reported in 1990 the results of their laser versus topical medications trial.[27] These showed a higher percentage of patients controlled by ALT alone at 1 and 2 years (63% and 44%) than by timolol alone (41% and 30%). But using any two of three allowed topical medications (timolol, dipivefrin, and pilocarpine) 85% and 66% of 'medical' eyes were controlled at 1 and 2 years respectively. The distinction between the two treatments becomes blurred when topical medications are added to failed ALT eyes and it is not easy to draw any firm conclusions. One could argue from the results that at 1 and 2 years medical therapy is better than ALT but the advantage probably lies with those patients who had ALT first because they were likely to avoid miotic therapy and its disadvantages for longer than those starting with timolol.

The advantages of surgery over ALT in controlling IOP are more clear cut. Both Watson *et al*[38] and Migdal and Hitchings[39] have confirmed the significantly lower pressures that can be achieved with trabeculectomy and the reduced need for subsequent medication.

Summary

Using the now well established technique ALT is a safe and effective means of lowering IOP in eyes with POAG, pigmentary glaucoma, and exfoliative glaucoma though the effect diminishes with time. Pressure reduction with ALT is seldom greater than 30% and eyes with an IOP of more than 28 mm Hg are unlikely to be controlled for any length of time without additional treatment. ALT is probably most suitable either for older patients whose glaucoma is not well controlled on medical treatment, or for patients with newly diagnosed open angle glaucoma, but without advanced field loss, as a primary treatment or in combination with a non-miotic topical medication. In many it will defer surgery, in some indefinitely.

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British Journal of Ophthalmology 1992; **76**: 627–629

CASE REPORTS

Bilateral multiple cavernous haemangiomas of the orbit

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Abstract

Orbital cavernous haemangioma, a common orbital tumour, is usually single and unilateral. We report the first case of histologically confirmed bilateral multiple cavernous haemangiomas of the orbit.

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Orbital cavernous haemangioma typically occurs as a slow growing well circumscribed lesion in the lateral part of the middle third of the orbit.[1] Patients most commonly present with slowly progressive painless proptosis or visual disturbance.[1-4] Though multiple lesions have been reported in the same orbit[1,2] we have traced only two reports of cavernous haemangiomas in both orbits.[5,6] We report the first case of histologically confirmed bilateral multiple cavernous haemangiomas of the orbit.

Case report

A 41-year-old Caucasoid woman noted a mass in the medial aspect of her right lower lid, in her late twenties. A plastic surgeon removed the lesion from her anterior orbit. Seven years later a violaceous lump in her left lower lid was also removed. Pathological examination of these lesions showed both to be typical cavernous haemangiomas.

Over the past 14 months she developed left proptosis, with intermittent swelling of the lower lid associated with a blue discoloration of the overlying skin (Fig 1). The swelling did not alter with changes in posture. She had no pain at any stage, and there were no associated visual symptoms. She was referred to one of us (JEW) for further evaluation.

Ophthalmic examination revealed a best corrected visual acuity of 6/9 OD, attributed to amblyopia, and 6/6 OS. There was 5 mm of left axial proptosis, and the left globe was displaced downwards 3 mm. Two small firm pea-sized masses were palpable, one on the anterior edge of the inferior orbital margin of the right orbit, and anteroinferior part in the left orbit. The rest of her ophthalmic examination was normal.

Computed tomography (CT) showed the orbits to be of normal size, although the right superior orbital fissure was bigger than the left. There was about 4 mm proptosis on the left. More than 20 small, rounded masses were seen in relation to the orbit, varying in diameter from 3 to 12 mm (Fig 2). Most of the retrobulbar lesions were intraconal, but similar masses were seen inferior to the globe, in the lids, and in the inferior orbital fissure. One relatively large lesion was contoured to the posteroinferior surface of the globe below the macula, and many lay along the optic nerve. At least 10 similar masses were present in the right orbit, predominantly anteriorly, below the globe. The rounded masses showed variable contrast enhancement. The superior ophthalmic veins were not adequately demonstrated, but the cavernous sinuses were normal. The appearances were considered typical of orbital varices.

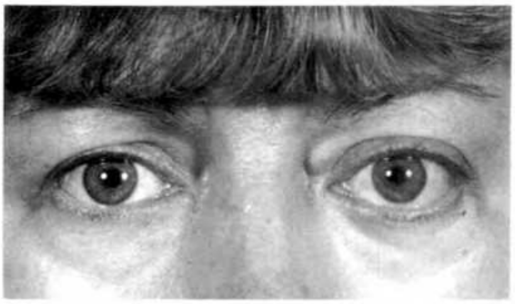

Figure 1 Clinical photograph showing left proptosis and the left lower eyelid swelling.

Intra-arterial digital subtraction angiography was carried out with injections into the left common, internal, and external carotid arteries (Fig 3). This showed small areas of pooling of contrast medium alongside the globe (supplied by the internal carotid) and posterosuperiorly in the orbit and overlying the maxilla (supplied by the external carotid). The left superior ophthalmic vein was not visualised.

A diagnosis of orbital varices was made and it was decided to remove the anterior component of the vascular anomaly in the left orbit. At operation three 10 mm diameter, discrete, raspberry coloured masses were removed from the extraconal fat of the inferior orbit.

Pathological examination revealed that all specimens had a similar appearance: wide, endothelial lined, blood-filled channels separated by fibrous trabeculae containing smooth muscle cells and surrounded by a capsule (Fig 4). The features were typical of cavernous haemangiomas.

Discussion

Cavernous haemangioma has been described as

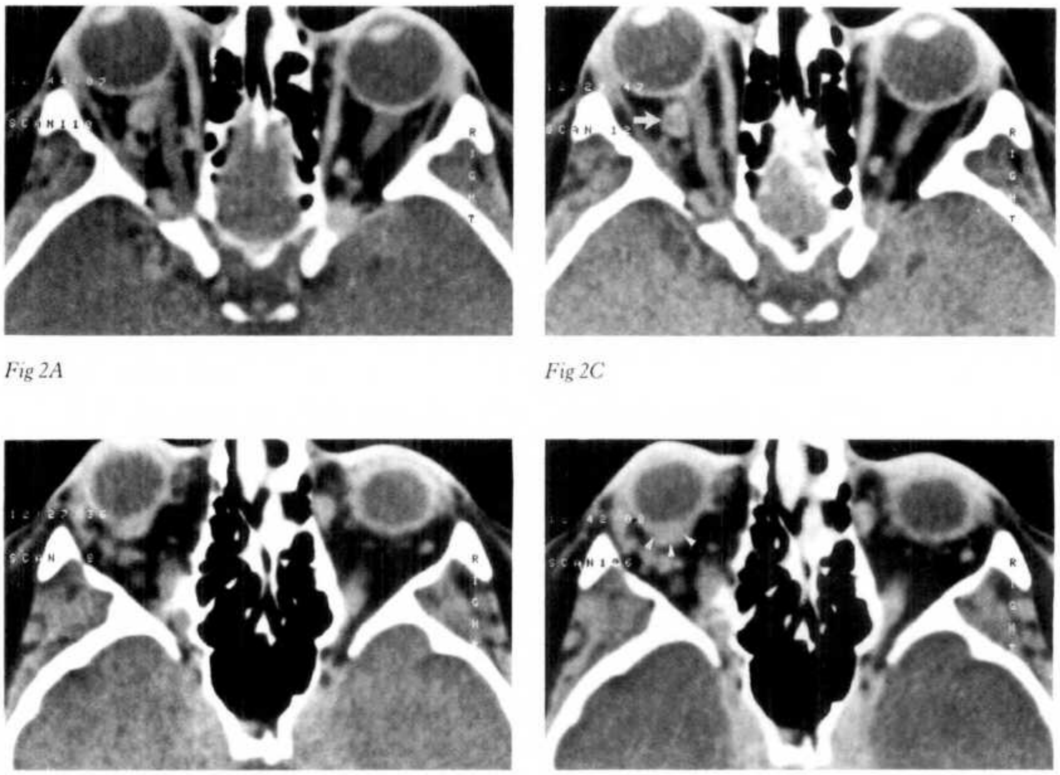

Fig 2A

Fig 2C

Fig 2B

Fig 2D

Figure 2 Axial CT (A,B) before (C,D) after intravenous contrast medium. Innumerable rounded or lobulated masses, 2–8 mm in diameter, lie in the retrobulbar spaces and surround the globes. One of the largest (arrowheads) is moulded to the posteroinferior surface of the left globe, while another (arrow) causes medial kinking of the distal portion of the left optic nerve. There is left proptosis.

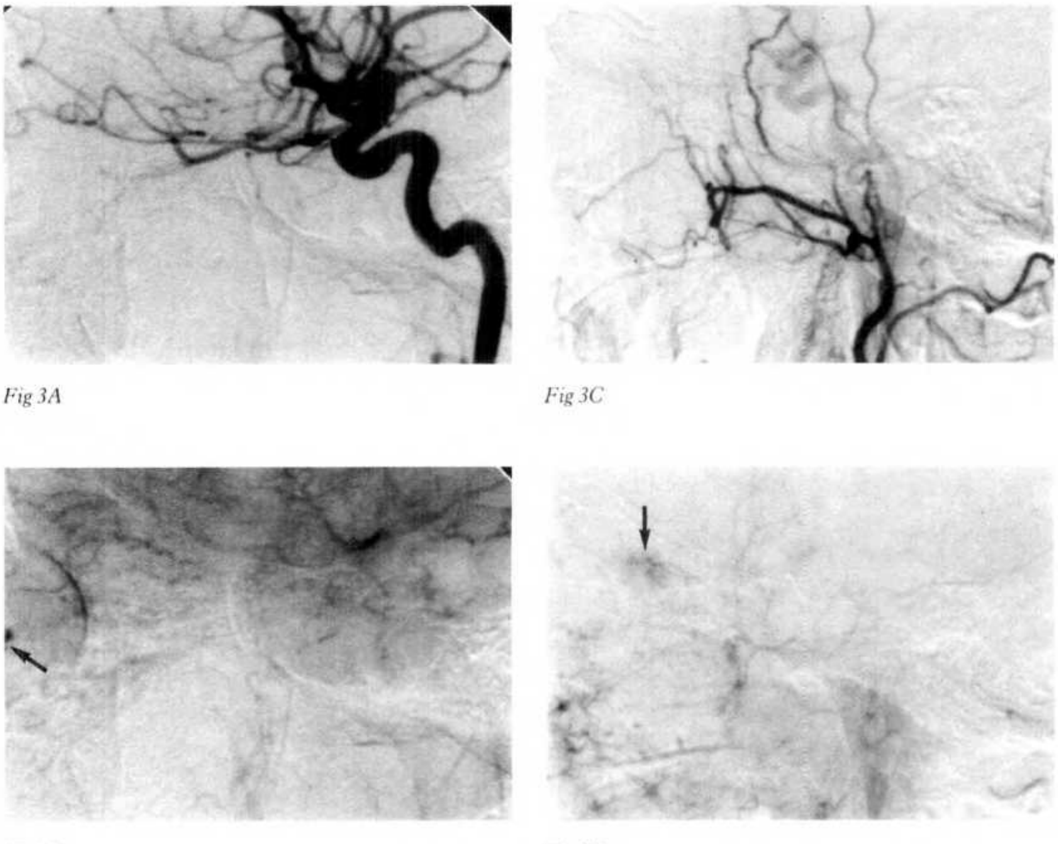

Fig 3A

Fig 3C

Fig 3B

Fig 3D

Figure 3 Digital subtraction angiogram, lateral projection (anterior to left). (A,B) Arterial and venous phases of left internal carotid and (C,D) similar phases of external carotid injection (with flash filling of internal carotid) show different small areas of

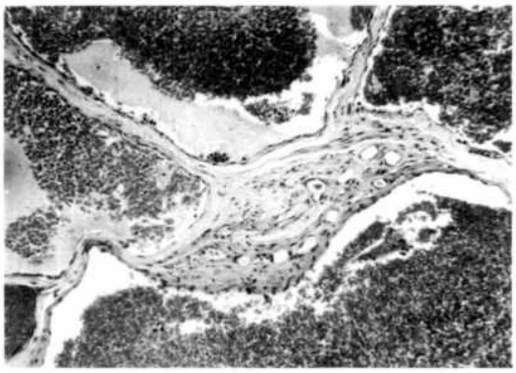

Figure 4 Histological appearance of the haemangioma removed from the left orbit, showing large blood filled channels separated by fibrous trabeculae. Frequently as here, the trabeculae are infiltrated by clusters of small capillaries (haematoxylin and eosin, ×80).

the most common orbital tumour.[7-9] The four principal reviews of cavernous haemangioma describe multiple lesions in the one orbit in none of six,[3] one of 13,[4] two of 66,[10] and five of 85 patients.[1] No cases of bilateral cavernous haemangiomas were seen in any of these large series, although two cases of presumed bilateral cavernous haemangiomas have recently been reported. Fries and Char obtained a tissue diagnosis from one orbit but did not operate on the contralateral orbit because of the paucity of symptoms on that side.[5] Johnson *et al* presumed a diagnosis of bilateral cavernous haemangiomas on clinical, ultrasonographic, and radiological grounds without obtaining tissue from either orbit.[6]

Our patient had an unusual history with multiple lesions, variable and intermittent lower lid swelling, as well as skin discoloration. Harris and Jakobiec reported one patient who had recurrent spontaneous upper lid ecchymosis.[10]

CT typically shows cavernous haemangiomas as well-defined rounded intraconal masses with smooth contours, of similar density to that of brain, which displace normal structures and enhance with intravenous contrast medium.[11,12] The differential diagnosis on CT includes peripheral nerve sheath tumours,[13,14] and rare lesions such as fibrous histiocytoma[14,15] or haemangiopericytoma.[4] The clinical, CT, and angiographic features in our patient were suggestive of primary orbital varices; the ophthalmologist should be aware of this variant.

It was not until surgery that the possibility of multiple cavernous haemangiomas arose. It is not clear why these characteristically unilateral, solitary lesions should have been multiple in both orbits in our patient. An association with Maffucci's syndrome (characterised by multiple enchondromas, soft tissue haemangiomas, and a generalised predisposition to neoplasia) and presumed bilateral orbital cavernous haemangiomas has been made.[6] But neither in our patient, nor that reported by Fries and Char, were there other stigmata of this disorder.[5]

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Lenticular burns following argon panretinal photocoagulation

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Abstract

Photocoagulation burns of the crystalline lens are a rare complication of posterior segment laser surgery. These burns occur more commonly in eyes with cataracts and with small, high-power, long-duration argon blue-green burns. We describe the first occurrence of lenticular burns caused by a fractured laser fibre optic cord.

(*Br J Ophthalmol* 1992; **76**: 630–631)

Photocoagulation burns of the crystalline lens are a rare complication of posterior segment laser surgery.[1-5] Focal white, cylindrical anterior cortical burns, which are usually non-progressive, appear immediately during the photocoagulation treatment. This complication is thought to be more common with long duration, high intensity, argon blue-green photocoagulation burns, though it has also been reported following krypton-red photocoagulation.[6] Focal anterior lens opacities have also been reported recently adjacent to inadvertent iris burns following indirect laser photocoagulation.[7]

We report a patient who suffered multiple lenticular burns owing to highly variable power output from a fractured laser fibreoptic cord.

Case report

A 60-year-old woman with diabetes mellitus of 20 years' duration was evaluated in October 1988 for diabetic retinopathy. Vision was 20/30 in each eye due to minimal bilateral nuclear sclerotic changes. Clinically significant macular oedema and mild background diabetic changes were seen in both eyes.

The macular oedema resolved following argon-green focal laser treatment and she did well until August 1990 when she developed peripupillary iris neovascularisation and proliferative diabetic retinopathy in both eyes. Vision was decreased to 20/40 in the right eye and 20/50 in the left eye due to mild progression of the bilateral nuclear sclerosis. One day prior to laser surgery the argon-krypton laser was serviced and upgraded to produce parfocal burns. Argon green panretinal photocoagulation was attempted in the right eye through a panfunduscopic contact lens using a 500 μm spot size and 0·2 second duration. Adequately intense retinal burns could not be obtained despite a maximal power of 1·10 W. Argon blue-green laser was then attempted with powers up to 2·23 W before retinal burns were obtained.

Visualisation of the fundus deteriorated during the course of the laser treatment and the procedure was discontinued after 241 burns had been applied. Multiple focal, cylindrical, yellow-white cortical lenticular opacities were seen when the contact lens was removed (Fig 1). These burns obstructed the visual axis and prevented any additional laser treatment. The fibreoptic cord connecting the laser with the slit-lamp delivery system was later found to be bent and internally fractured. Minimal fibreoptic movement resulted in widely variable burn intensities. The machine was again serviced 1 day after the photocoagulation treatment. The laser produced parfocal and accurately sized burns. However, the power output varied between 25–100% of the selected power depending on movement of the fibreoptic cord. The fractured cord was removed from the laser suite by the servicing technician for later analysis.

Vision in this eye 2 weeks later was 20/200 with essentially no change in the cortical opacities. Phacoemulsification with placement of a posterior chamber intraocular lens was performed on 17 September 1990. Panretinal photocoagulation was then completed in both eyes over the next 2 months. All iris and posterior segment neovascularisation subsequently involuted. Vision 1 year following cataract surgery in the right eye was 20/40.

The manufacturer has informed us that they were unable to carry out an in depth visual inspection of the cord because the removal of plastic coating from the underlying fibreoptic was not possible.

Discussion

The fractured fibreoptic cord produced highly variable power outputs during our patient's laser

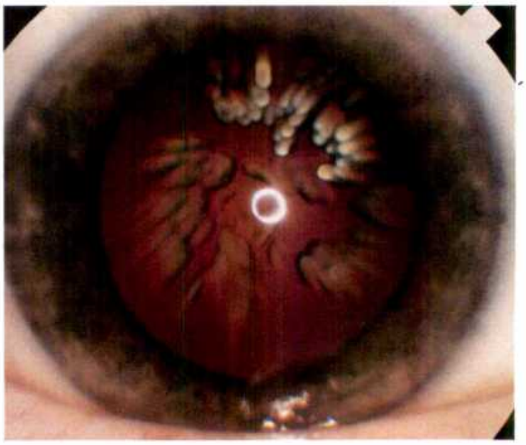

Figure 1 Multiple cortical lenticular burns immediately following argon panretinal photocoagulation.

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treatment. Powers of up to 2·23 W were selected, but this delivered powers to the cornea varying from 0·56 to 2·23 W. We postulate that initially the laser machine was delivering a much lower power than was selected. At some point during the treatment, possibly after switching to argon blue-green, the fibreoptic cord may have shifted and produced a firmer contact between the fractured ends. This caused a much more intense burn to be delivered to the eye and resulted in the focal lenticular burns described above. Our patient's pre-existing nuclear sclerotic cataract may have predisposed her to developing this complication.

Several precautions should be taken to prevent laser-induced lenticular burns. Small, long-duration, high-power, argon blue-green burns should be avoided if possible. This is especially true in the presence of a nuclear-sclerotic cataract. In addition, the laser surgeon should be aware that inability to obtain adequately intense or variably intense retinal burns may be caused by a fractured fibreoptic laser cord. Adequate precautions should be taken in the laser suite to protect this cord from injury. In addition, careful preoperative checking of the laser should be made after every service call.

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Bilateral congenital mydriasis

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Abstract

A single case of bilateral congenital mydriasis is described. A review of the literature is presented and possible modes of inheritance are discussed.

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Congenital mydriasis is an extremely rare ophthalmic condition. By definition the fixed and dilated pupils are present from birth and occur in an otherwise normal seeing eye.[1 2] All previously reported cases are bilateral and have occurred in females. We report the clinical findings of a 2½-year-old girl who has congenital mydriasis and developmental delay. The condition of congenital mydriasis should be considered separate from aniridia both in clinical appearance and visual potential.

Case report

A 2½-year-old girl was referred with the diagnosis of general developmental delay and bilateral congenital, fixed, dilated pupils. The girl was born at term after an uneventful pregnancy and delivery. From birth the mother noted dilated, unreactive pupils. The child's main problem was developmental delay. The infant was floppy and was late in achieving her motor milestones. Visually the child also seemed delayed. She did not smile to a visual stimulus until 6 months of age. The parents became concerned at this stage and consulted an ophthalmologist who ordered an ERG which was normal.

A fine horizontal nystagmus was present during infancy which has diminished with time such that no nystagmus was detected at age 2½ years. Concurrent with the reduction in nystagmus has been an improvement in her visual function.

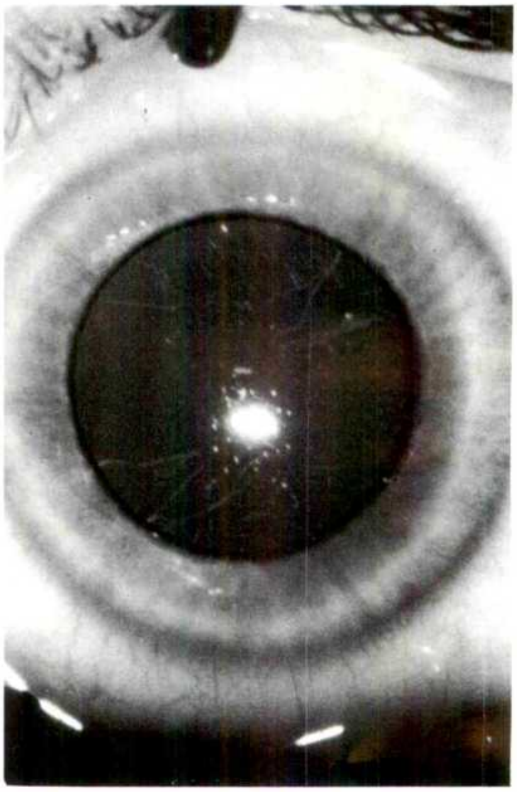

Figure 1 Rim of iris seen with pupillary ruff. Fine pupillary membrane present.

There is no family history of note, no consanguinity of the parents, and the child has a healthy 4-year-old sister. At the time of the examination at age 2½, the mother felt her child was seeing normally. The parents thought that the child was light sensitive, though this was not borne out when the examination took place. The general examination was normal. (Formal assessment of motor and social skills by Griffith's

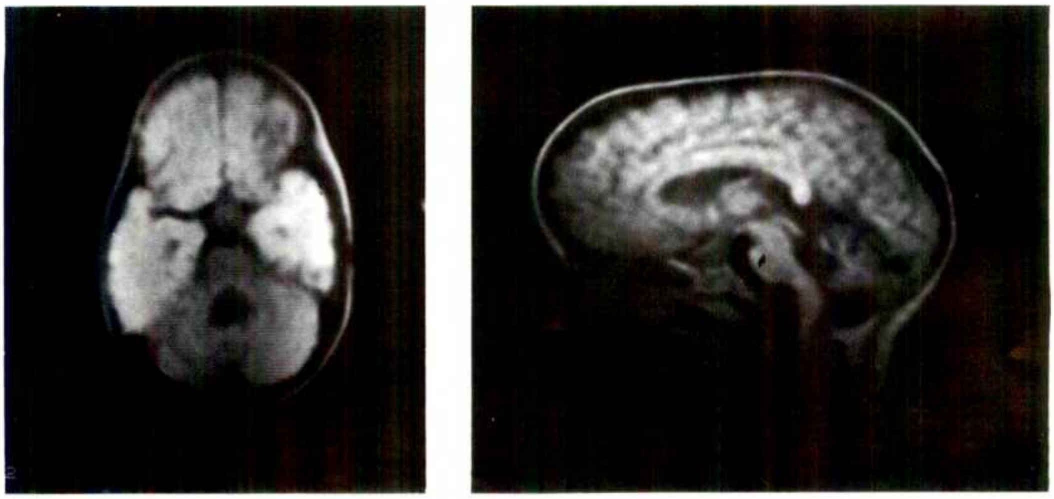

Fig 2A

Fig 2B

Figure 2 Transverse (A) and sagittal (B) spin-echo (SE 544/44) images of the brain showing an enlarged fourth ventricle, atrophic vermis of the cerebellum, and normal aqueduct and midbrain. The left lateral ventricle was slightly dilated on high images (not shown).

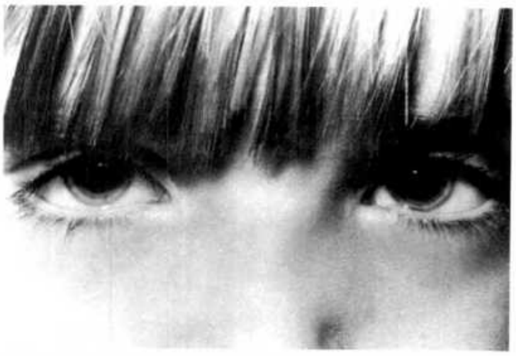

Figure 3 Pupil size before pilocarpine.

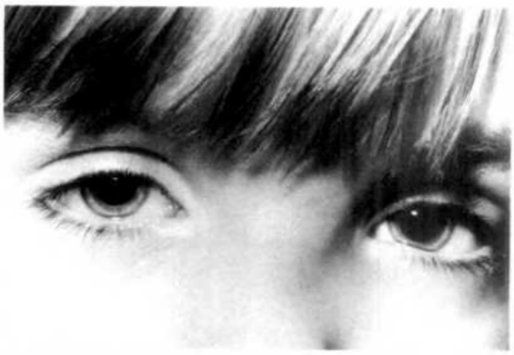

Figure 4 Pupil size 60 minutes after pilocarpine.

scoring revealed a level achieved of 15 months when the child was aged 30 months.) The pupils were dilated and unreactive to light or the near reflex. The pupil diameter was 7 mm and round and symmetrical. The irises themselves were grossly normal in appearance. There was a reasonable rim of iris and a fine, persistent pupillary membrane (Fig 1). The cornea, lens, vitreous, optic nerve, macula, and peripheral retina were entirely normal on examination. Corneal diameter was 12·5 mm left and right, intraocular pressures, right 9 mm Hg, left 8 mm Hg. An examination under anaesthetic was performed; the angle architecture was normal on gonioscopy. A patchy transillumination defect of the peripheral iris was noted on examination with the operating microscope.

The child was extensively investigated and urinalysis was normal. There was no haematuria; urea and electrolytes, osmolarity, urine amino acids, organic acids, blood gases, plasma lactate, and chromosome studies were all normal. A pattern evoked ERG was performed which was normal, and occipital VEPs to pattern reversal stimulation were evident from each eye for medium sized checks. CT scan and MRI brain scan did show an enlarged fourth ventricle, some hypoplasia of the vermis of the cerebellum, and a normal midbrain (Fig 2). Attempts were made to constrict and dilate the iris with pilocarpine and atropine respectively; however, photographically, no change was discernible (Figs 3 and 4).

Discussion

Eleven cases of bilateral congenital mydriasis have been reported previously in the literature; all 11 are female. The first two cases reported by White and Fulton[1] occurred in monozygotic twins and the eye abnormality was described as large, irregular pupils which reacted only slightly to light. The authors suggested that the abnormality was due to congenital absence of the sphincter iridis. Although not examined, the twins' mother was also said to have a similar iris anomaly suggesting a dominant inheritance.

Caccamise and Townes[2] reported a single case of congenital mydriasis and on the patient's evidence identified seven other members of the family with similar findings. No males were found to have congenital mydriasis. The authors agreed with White and Fulton that the likely mode of inheritance was autosomal dominance. The authors pointed out that some form of sex limitation such as occurs in incontinentia pigmenti either X chromosome linked or autosomal dominant with non-viability of males could not be excluded. Our case, also female, strengthens the sex limitation theory for the mode of inheritance. Caccamise and Townes found slight pupillary constriction to light and pilocarpine, and dilatation to phenylephrine 10%. They agreed that the iris sphincter and dilator were present. We were unable to identify any pupil constriction to pilocarpine (Figs 3 and 4).

Our patient was referred by non-ophthalmologists with the presumptive diagnosis of aniridia. The child has none of the ocular features of aniridia and the iris structure itself appears normal albeit in a fixed, dilated state. Sporadic cases of aniridia are associated with Wilm's tumour and aniridic eyes typically have poor vision. There is no evidence of these associations in congenital mydriasis and the distinction between the two conditions should be clear.

Summary

A case of bilateral congenital mydriasis is presented in a 2½ year-old child with developmental delay. All previously reported cases have been female. Our case, also female, further supports the theory of a form of sex limitation with non-viability of males as the mode of autosomal dominant inheritance. The visual potential in this condition is normal and a clear distinction from aniridia should be made.

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Myoepithelioma of the lacrimal gland: report of a case with spindle cell morphology

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Abstract

The case is described of a 23-year-old female patient presenting with unilateral proptosis, headaches, and transient epiphora. Surgery revealed an encapsulated tumour composed exclusively of spindle-shaped cells within a richly vascularised myxoid stroma. Immunohistochemical staining showed focal positivity for smooth muscle actin, vimentin, and glial fibrillary acidic protein. These combined findings are interpreted as providing evidence of a myoepithelioma, which may be regarded as a monomorphic adenoma consisting solely of myoepithelial cells. To our knowledge this is only the second report of such a tumour in the lacrimal gland.

(*Br J Ophthalmol* 1992; **76**: 634–636)

It may be that most benign adenomatous tumours of the lacrimal gland are derived from the myoepithelial component of the parenchyma. These cells differentiate to produce unmistakeable epithelial and, frequently, overtly glandular structures as well as, in the vast majority of instances, a variably hyaline, myxoid, or chondroid extracellular stroma. The resultant tumour is then aptly named a pleomorphic adenoma, and in this respect the lacrimal gland parallels its salivary counterpart. Occasional salivary gland adenomas, however, are monomorphic in that fully differentiated ductular or duct-derived epithelium alone is seen, while even more unusually the tumours are restricted to a myoepithelial proliferation with an absence of manifest glandular components. Monomorphic adenomas arising in the lacrimal gland are still rarer: tumours with a uniform glandular pattern have yet to be described and there has been only one previous report of a pure myoepithelial proliferation.[1] Here we describe a second case.

Case report

A 23-year-old woman presented to the orbital clinic of Moorfields Eye Hospital complaining of gradually increasing proptosis of her left eye. She had been conscious of some 'puffiness' around the eye for up to 1 year and for the last 3 months had suffered occasional left parietal headaches and transient epiphora. Ophthalmic examination revealed 5 mm proptosis with 2–3 mm downward displacement of the left eye and there are some restriction of eye movement on upgaze, particularly in abduction. Visual acuity was not affected (RE 6/6; LE 6/4) and the ocular fundi were ophthalmoscopically normal. A mass could be palpated in the left lacrimal fossa and ultrasonography produced abnormal echoes temporal to the globe, both superiorly and inferiorly.

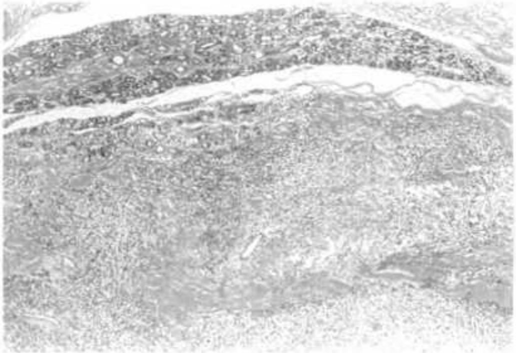

Figure 1 Histological section showing elongated lobules of atrophic lacrimal gland tissue adjacent to the capsule of the tumour (haematoxylin and eosin, ×32).

The preoperative clinical diagnosis was lacrimal gland tumour, probably benign, and 7 weeks later a circumscribed and apparently encapsulated mass was excised through a left lateral orbitotomy. There was no detectable involvement of the adjacent periosteum and the postoperative course was uneventful.

At the present time, more than 12 years after surgery, the patient is alive and well with no sign of recurrent tumour.

Pathology

Grossly, the resected tumour showed a smooth, encapsulated, pale grey, firm and reniform mass measuring approximately 30×25×17 mm. Microscopically, the mass was covered by a fibrous capsule enclosing a solid tumour composed exclusively of spindle-shaped cells. Lobules of atrophic lacrimal gland tissue were confined to one edge of the tumour adjacent to its capsule (Fig 1). Most of the tumour cells had rounded or elongated nuclei according to the

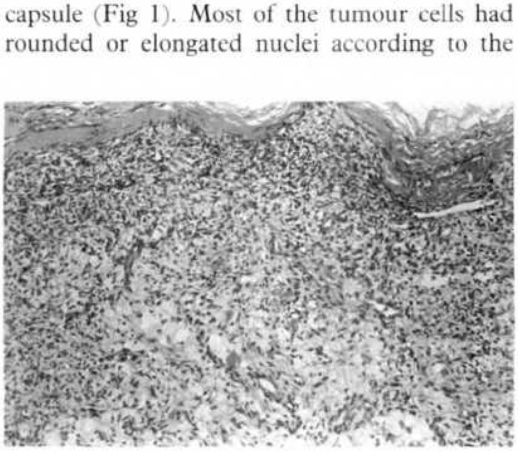

Figure 2 The lacrimal gland mass is covered by a fibrous capsule and consists of spindle-shaped cells intermixed with numerous capillaries (haematoxylin and eosin, ×80)

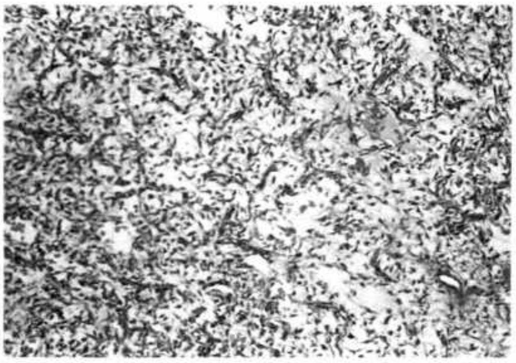

Figure 3 The centre of the tumour is similarly composed of spindle-shaped cells with thin, elongated, cytoplasmic processes embedded in a myxoid matrix rich in capillaries (haematoxylin and eosin, ×80).

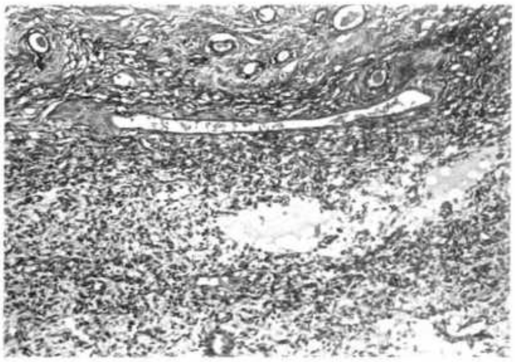

Figure 5 The capsule of the tumour seen in the upper part of the photomicrograph, includes several lacrimal gland ducts, while the underlying tumour shows cohesive perivascular cells alternating with loose areas consisting of proteinaceous exudate (Masson trichrome, ×80).

cellular orientation with inconspicuous nucleoli but occasionally slightly enlarged and hyperchromatic nuclei were also seen. Mitotic figures were rare. The cell cytoplasm was either eosinophilic or vacuolated, especially in less densely populated parts of the tumour where a prominent myxoid stroma was observed (Figs 2 and 3). A rich capillary network with scattered large sinusoidal vessels was present. In some areas the tumour displayed confluent cystoid spaces containing proteinaceous exudate and occasional erythrocytes (Fig 4). The loose myxoid areas alternated with dense aggregates of spindle cells, some of which demonstrated a perivascular arrangement (Fig 5). Areas of necrosis with secondary haemorrhage were present and in places this appeared to have been superseded by hyaline fibrous tissue.

Immunohistochemical procedures using a peroxidase-antiperoxidase method demonstrated focal response of some cells with antibodies against smooth muscle actin, vimentin, and glial fibrillary acidic protein (GFAP). Labelled antibody to low molecular weight keratin (AE1) stained the residual lacrimal ducts adjacent to the capsule of the tumour but the spindle cells were unreactive (Fig 6). Negative staining reactions were obtained using antibodies to S-100 protein.

Discussion

It is a common finding that a proportion of pleomorphic adenomas in both the salivary[2] and the lacrimal[3] glands contain solid foci of myoepithelial cell proliferation. The validity of a diagnosis of myoepithelioma, however, depends on demonstrating that the tumour is essentially monomorphic and that the constituent cells are myoepithelial. While this can reasonably be construed from the shape of the cells in the present case, the diagnosis is rendered more secure by the evidence that a proportion of the spindle-shaped cells contained smooth muscle actin. Grossniklaus and colleagues,[4] in an immunohistochemical study of normal and neoplastic lacrimal gland tissue, found that myoepithelium in situ at the perimeter of normal secretory acini reacts strongly with antisera to smooth muscle actin, rarely with antibodies to GFAP and strongly but inconsistently with a wide spectrum of antikeratin antibodies. The same study showed that a minority of the spindle-shaped stromal cells in pleomorphic adenomas were positive for smooth muscle actin, while rare stromal cells stained weakly for vimentin. In their study, positive reactions for keratin and GFAP were associated with a proportion of so-called epithelioid as opposed to spindle-shaped myoepithelial cells. A weak response for GFAP was the sole positive immunohistochemical staining seen in the other case of lacrimal gland myoepithelioma.[1] It would seem, however, that caution must be used in the interpretation of such data. Thus, although GFAP reactivity has been used as a criterion for the identification of myoepithelial cells, it was positive in only two of 23 normal salivary glands in one extensive study.[5] Similarly, S-100 protein,

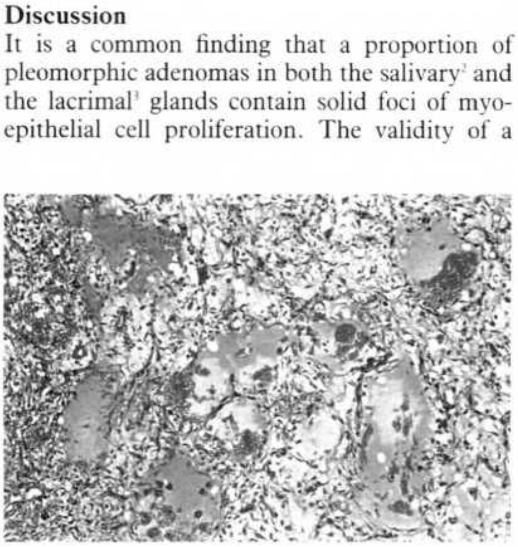

Figure 4 In other areas the mass exhibits cystoid spaces containing proteinaceous exudate and erythrocytes (Masson trichrome, ×80).

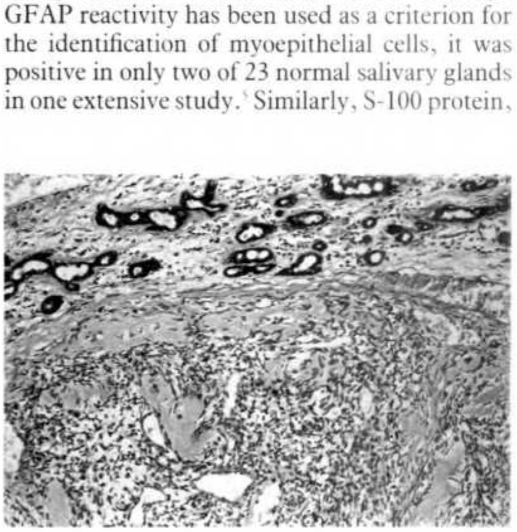

Figure 6 Section of an area adjacent to that seen in Figure 5 showing lacrimal gland ducts immunoreactive for cytokeratin (brown-black), in contrast to the underlying spindle cells which are negative (low molecular weight keratin AE1, ×80).

the S-100b form of which has formerly been regarded as a marker for myoepithelium,[6] has more recently been shown to be confined to closely associated autonomic nerves within the glands.[7] That being the case, the negative reaction for S-100 protein in both our patient and that of Heathcote and colleagues[1] is not contrary to a diagnosis of myoepithelioma.

Ultrastructural characteristics of myoepithelial cells, such as micropinocytotic vesicles, cytoplasmic filaments consistent with actin and a pericellular basement membrane, have been described in myoepithelial tumours of the salivary glands[8] and in the one recorded lacrimal gland example of this type of tumour.[1] We believe, however, that these are not pathognomonic features and are not essential for the diagnosis and note that Dardick and others[8] defined myoepitheliomas solely on the basis of their light microscopic and immunohistochemical properties. We contend, therefore, that it is reasonable to regard the present tumour as a spindle-cell myoepithelioma and, despite the finding of occasional cells with abnormal nuclei, to have anticipated a benign prognosis borne out by the patient's 12-year trouble-free postoperative survival.

The potential for a variety of adenoma types, ranging from pure ductal proliferations (monomorphic type) through lesions of mixed cell type to pure myoepithelial tumours, to be seen in the lacrimal gland is readily appreciated on the assumption that, as has been reasoned in the context of the salivary glands,[5] they all originate from a common precursor. Whether or not that precursor is myoepithelial, as has generally been assumed, is not clear because of inconsistent and potentially ambiguous immunohistochemical marker findings. It is also reasonable to assume that most adenomas will occupy the mid-range of the spectrum and be mixed tumours, though it might be wondered why the extremes are encountered less frequently in the lacrimal gland than in the salivary glands. Using the salivary tumours as a guide, however, there is no cause to regard monomorphic adenomas, including myoepitheliomas, as having a different biological behaviour from the more usual pleomorphic lesions.[9] This is a point of some importance because myoepitheliomas involving the salivary glands have quite often been diagnosed as malignant tumours,[10] as for a time was the present case. As applied in the salivary gland context, a number of morphologically different subtypes of myoepithelioma are described with 90% consisting of spindle-shaped or polygonal cells.[8] We believe that both Heathcote and colleagues' case and ours, are examples of pure spindle cell myoepithelial tumours. Additionally, there is a third case recorded by Rootman[11] which we suspect represents the same entity.

We are grateful to Mr John Wright, Moorfields Eye Hospital, for access to the clinical information.

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British Journal of Ophthalmology 1992; 76: 637–638

Vanishing retinal arterial aneurysms: a case report

Sarah L Owens, Zdenek J Gregor

Abstract

An 18-year-old woman with retinal vasculitis developed multiple retinal arterial aneurysms over a period of 3 years. Subsequently she developed macular oedema, peripheral neovascularisation, and vitreous haemorrhage and was treated with systemic steroids, laser photocoagulation, and vitreoretinal surgery. No systemic cause for vasculitis was found. Serial fluorescein angiography demonstrated gradual resolution of the arterial aneurysms over the subsequent 7 years.

(*Br J Ophthalmol* 1992; **76**: 637–638)

An 18-year-old Asian Indian woman was seen in August 1984, complaining of poor vision in the right eye for the past year. Her first complaint of visual difficulty occurred in 1981; at that time she was managed at another hospital for retinal vasculitis. A fluorescein angiogram from 1981 showed peripheral retinal vascular leakage but documented normal retinal vascular calibre (Fig 1).

On initial examination visual acuity was 6/36 in the right eye and 6/6 in the left eye. Both anterior chambers had mild cell and flare. Funduscopic examination revealed minimal disc swelling in both eyes. The most striking feature was the presence of multiple retinal arterial aneurysms (Fig 2). A fluorescein angiogram disclosed severe peripheral non perfusion (Fig 3). A comprehensive systemic work-up was unrevealing, and a diagnosis of atypical vasculitis was made.

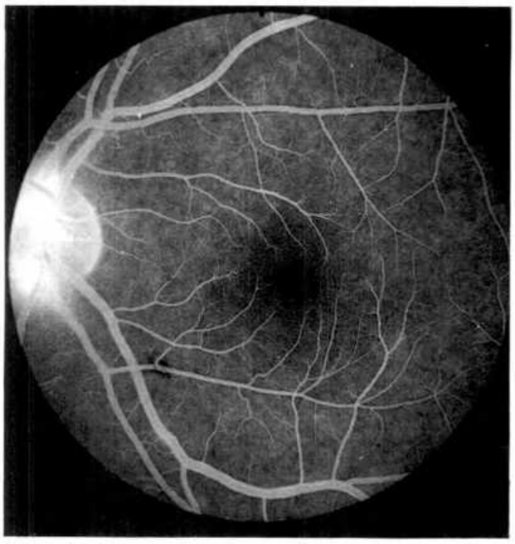

Figure 1 Fluorescein angiogram, late arteriovenous phase, left eye, 1981. Note normal calibre of retinal arterial system.

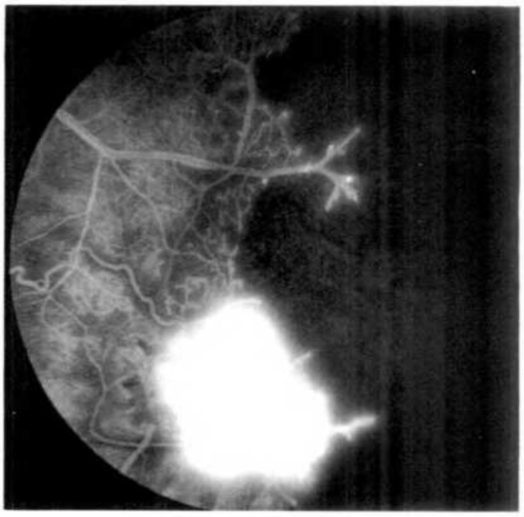

Figure 3 Fluorescein angiogram, venous phase, left eye, 1984. Note severe peripheral non perfusion with leakage from adjacent retinal neovascularisation.

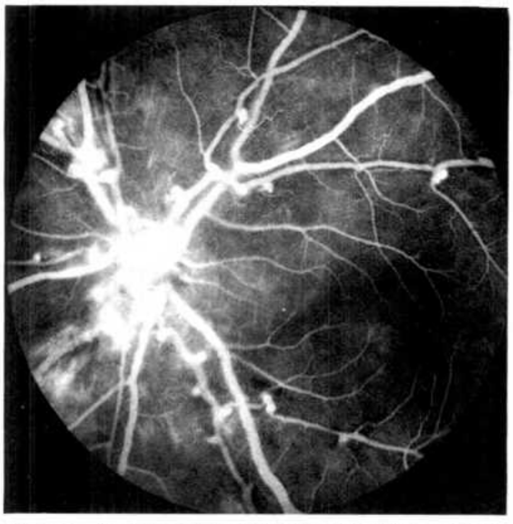

Figure 2 Fluorescein angiogram, mid arteriovenous phase, left eye, 1984. Note multiple retinal arterial aneurysms and disc neovascularisation.

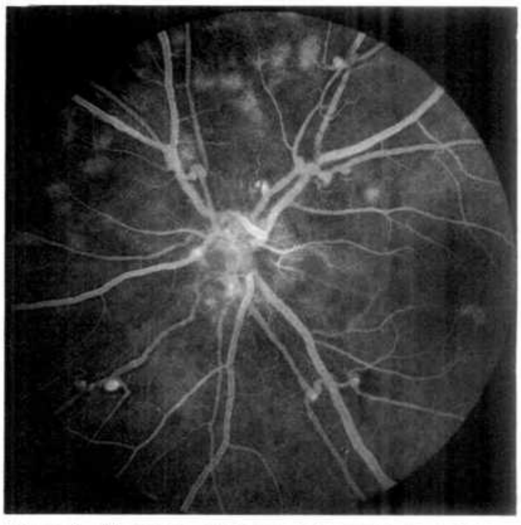

Figure 4 Fluorescein angiogram, late arteriovenous phase, left eye, 1990. Note resolution of some aneurysms, particularly of the inferotemporal branch artery when compared with Figure 2.

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She was treated initially with high-dose systemic steroids and panretinal photocoagulation in both eyes. However, despite treatment her visual acuity decreased to hand movements in the right eye. She subsequently suffered a vitreous haemorrhage in the right eye; vitrectomy was performed in October 1987. By early 1988 her disease became quiescent with no medication. She reached a final visual acuity of 6/60 in the right eye and 6/6 in the left eye 9 years after the onset of her disease. Throughout this period there was a gradual decrease in the size and number of retinal arterial aneurysms. This was documented by the most recent angiogram (Fig 4).

Discussion

Three cases of retinal vasculitis and multiple retinal arterial aneurysms have been reported.[1 2] The appearance and subsequent regression of these abnormalities has not been reported previously.

Aetiological considerations include infection, connective tissue disorders, degenerative retinal disease, and neoplasia. Rarer causes of vasculitis primarily affecting arteries (as in our case) include polyarteritis nodosa, systemic lupus erythematosus, Goodpasture's syndrome, Churg Strauss syndrome, and Loeffler's eosinophilic syndrome.[3]

As in the other cases of multiple retinal arterial aneurysms reported in the literature, our patient was young and otherwise well. A comprehensive work-up in our patient was unrevealing. No systemic disorder developed during 10 years' follow-up.

In contrast to the other reported cases our patient suffered substantial retinal exudative and ischaemic complications during the long follow-up period. This case also demonstrated the hitherto unreported reversibility of the aneurysms once the disease became quiescent. The underlying mechanisms for this process remain unclear.

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LETTERS TO THE EDITOR

Sir William Bowman

EDITOR,—The recent editorial on Sir William Bowman[1] leads to two points worthy of mention, for their continuing relevance to medicine today.

Firstly, it seems that no one completes a distinguished medical career without *some* dispute and William Bowman was no different in this respect. Argument arose over Bowman's discovery of the essentially muscular nature of the 'ciliary membrane' in 1823, as a paper on the same subject had been presented a year previously by Robert Knox – he of the infamous connection with Burke and Hare (who were hanged for the crime of murdering vagrants to procure corpses for dissection).

Knox's paper included study of the ciliary muscle in vultures, in which it was very strong, in horses and deer, in which it was less marked, and in fishes, in which it was rudimentary. Apparently his association with Burke and Hare had turned him away from human anatomical study for a while, but in any case the debate over whether the credit was due to Bowman or Knox continued for years.[2]

Another salutary point is Bowman's example of fostering good medical nursing relations. Florence Nightingale's *initial* crusade was for better standards of nursing in Britain, since nurses of the time were often drunk on duty and tended to combine their duties with prostitution.[3]

Bowman, impressed with her assistance at a difficult operation, became her 'mentor' and offered her the chance to re-organise nurse training at King's College Hospital. Although this never came about, owing to Miss Nightingale leaving for the Crimean war, the example of interdisciplinary cooperation is one we could probably learn from today.

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Acyclovir in herpes zoster ophthalmicus

EDITOR,—I read with great interest the article by Marsh and Cooper.[1] Herpes zoster ophthalmicus (HZO) is indeed a serious illness, often characterised by severe ocular complications. Better knowledge on how to manage HZO complications by properly designed studies, such as the one by Marsh and Cooper, is therefore highly desirable. However, when dealing with HZO it is extremely important to distinguish between two different situations: acute HZO (a skin rash of equal or less than 3 days' duration) and late (subacute or chronic) HZO (with a rash of more than 3 days' duration), as the therapies differ radically. In the study by Marsh and Cooper we are clearly in the second situation of late HZO, as patients were included up to 3 weeks after the skin rash had appeared. It is interesting to note that the results of the study confirm the prevailing clinical impression that steroids are (most of the time) indispensable for treatment of ocular inflammatory complications of HZO when it was not treated with systemic acyclovir (ACV) in the acute phase. The currently admitted rationale is, as the authors state, that inflammation is probably produced by antigenic changes of damaged tissue and not by viral replication.

The situation is however completely different in acute HZO where active viral replication is at the origin of disease morbidity. Moreover, the strong antibody response seen in HZO indicates that it is not a purely ocular phenomenon but has a systemic component, probably because varicella zoster virus (VZV) also spreads along perineural and perivascular pathways.[2] It is therefore reasonable to administer systemic ACV which, at the oral dose of 800 mg five times daily, is known to inhibit replication of most VZV strains.[3]

We showed in a series of 48 patients, treated with adequate doses of oral ACV within 3 days of skin eruption, that no patient went on to a chronic course or needed steroid therapy within a minimum follow-up period of 2 years.[2] We further showed that, if only topical or inadequate systemic doses of ACV were given, the rate of serious ocular complications or chronic evolutions tended to be equal to the pre-ACV rate of plus or minus 20%.[4] The body of clinical evidence presently available, indicating that systemic doses of ACV given within 3 days of skin eruption prevent serious ocular complications, is so patent that, on an ethical base, no patient should at present be denied such treatment.[5-8] The financial implications of routine ACV therapy for all cases of acute HZO are not to be minimised. However it is far from certain that the health cost of HZO will be cheaper if the decision is made not to treat systemically. We found that the average treatment duration and average number of visits of the group of adequately treated acute HZO patients was respectively 23 days and 5·5 visits, whereas it was 90 days and 10·1 visits in a group of patients having received only topical or inadequate systemic ACV (late treatment or insufficient doses). If prolonged therapy, prolonged medical care, and job absenteeism are taken together, routine systemic ACV therapy might well be more cost efficient.

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1 Marsh RJ, Cooper M. Double-masked trial of topical acyclovir and steroids in the treatment of herpes zoster ocular inflammation. *Br J Ophthalmol* 1991; 75: 542–6.
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Reply

EDITOR,—We were interested to read Dr Herbort's letter. Whilst we agree about the importance of delivering effective systemic antivirals at the start of the disease, it is very seldom possible to do so. The vast majority of patients present to doctors when the rash is established and viral replication has been going for at least 5 days and has scattered throughout the tissues of the dermatome involved. Therefore most patients have secondary inflammatory complications at presentation. As far as the efficacy of systemic acyclovir is concerned, we are aware at present of only one controlled trial with administration of systemic acyclovir within the first 72 hours which claims a reduced instance of ocular complications.[1] The remaining series of reports are a mixture of prospective and retrospective results and are not double blind and controlled. We still feel that it is necessary to have another blind controlled trial with random selection of patients within 72 hours of the onset of pain with no exclusion of those with ocular complications at presentation (which occurred in the Cobo series).

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1 Cobo LM, Foulks GN, Liesegang TJ, Lass J, Sutphin JE, Wilhelmus K, *et al.* Oral acyclovir in the treatment of acute herpes zoster ophthalmicus. *Ophthalmology* 1986; 93: 763–70.

BOOK REVIEWS

Developments in Ophthalmology, Vol 19. **Ultrastructure of the Conjunctival Epithelium.** By Klaus-Peter Steuhl. Pp 104. £40.00. Karger: Basel, Switzerland, 1989.

Recognition of the importance of the conjunctiva and Tenon's capsule in ocular disease and wound healing is increasing. As knowledge of conjunctival anatomy and physiology grows an understanding of its pathology becomes clearer. It is the surface epithelium of the conjunctiva (and cornea) which is first exposed to external factors within the precorneal tear film. It also has a role in synthesising components of the precorneal tear film and thus both affects and is affected by the tear film. A detailed study of the conjunctival epithelium is therefore fully justified and is well presented in an organised fashion in this book.

The author sets out to explain the morphological significance of known and proposed functions of the conjunctival epithelium. In the introduction he provides a brief but well referenced synopsis on conjunctival/tear film structure and function. In contrast the chapter on materials and methods, although comprehensive, is of little direct interest to the general ophthalmologist. Most of the book is devoted to the results of the author's morphological study of both animal and human tissue. This is well illustrated with electron and light micrographs. A classification of five surface epithelial cell types, based on ultrastructure, is proposed for the first time. This may prove to be an overclassification but is difficult to criticise on the evidence presented. Regional and age-related differences in the distribution of these cell types are thoroughly investigated as are changes in the epithelial ultrastructure in Sjögren's syndrome, after lime burns, and following chronic treatment with topical antiglaucoma drugs. The studies on pathological tissue can be criticised since only small numbers are investigated but this should not detract from their interest. Conjunctival resorption processes and corneal re-epithelialisation are also explored. The discussion is well documented and relates the morphological findings to function and pathological processes.

In summary this is an interesting piece of work, highly detailed, but also highly specialised. This makes it an important volume for the researcher or specialist with an interest in the conjunctiva but it is of less relevance to the general ophthalmologist.

DAVID BROADWAY

Cataract Surgery: Alternative Small-Incision Techniques. Edited by George W Rozskis. Pp 194. £76.50. Slack: Beckenham, Kent. 1990.

This is a most interesting book which is clearly written and well illustrated with numerous step-by-step drawings. It comes with the added bonus of a videotape showing each author's particular procedure.

The main purpose of the book is to show how cataracts may be removed through small posteriorly placed incisions which minimise astigmatism without resorting to phakoemulsification and thus avoid the drawbacks of learning curve, expense, and reliance on mechanisation.

The first chapter deals with a review of the causes of astigmatism and the rationale and techniques for a scleral pocket incision with a good discussion of the pros and cons, mentioning relevant complications and their avoidance.

There are three chapters devoted to removal of the nucleus, either by traction in which it moulds through the section, or after division into two fragments by a guillotine action of two instruments or division by a small snare: the fragments are then removed with a modified loop or forceps.

There is a chapter on hydrodelineation of the nucleus whereby the nucleus is fragmented by hydrodissection into multiple concentric rings. For anything other than relatively soft lenses, ultrasonic assistance is required to enable the 29 gauge cannula to pass through the lens.

Another chapter describes utilisation of partial phako-emulsification with extraction of nuclear fragments through a small section using instruments or pushing them out on a wave of viscoelastic.

As with any other book, there are parts which are more instructive, better reasoned and more interesting than others, but all in all it is a most interesting package of book and video. Both are complementary as a 'picture is worth a thousand words' but the text is required to explain the whys and wherefores of the procedure.

J JAGGER

A Text and Atlas of Strabismus Surgery. By Renée Richards. Pp 226. £75.00. Chapman and Hall: London, 1991.

This book, in the Chapman and Hall *Medical Atlas* series, is, as the title indicates, an attempt to combine a didactic text with an illustrated account of strabismus surgery. We are assured by the text on the rear cover that the book 'describes principles, indications, and techniques of surgery on the extrao-cular [*sic*] muscles'. We are further assured that 'actual techniques' are included and that the combination of text and illustrations 'targets readership at residents and graduates in ophthalmology'.

Dr Richards practises in New York but the book appears to use English spellings where they differ from the American form, for example anaesthesia, anaemia. In contrast to this, standard English definitions such as that for consecutive exotropia are not used. Dr Richards also uses an unusual form of English which this reviewer found disconcerting. Wherever the concept of 'yoke muscles' (that is – a pair of synergists pulling together in the fashion of oxen or horses yoked together) is raised the text uses the spelling 'yolk'. On page 74 there is reference to patients with Brown's syndrome adopting a 'vicarious head position.' My dictionary defines vicarious as meaning 'done on behalf of another.' On page 75 we are introduced to 'trebacles' between the superior oblique tendon and its hypothetical sheath. On page 138 the eye is said to 'tort' under general anaesthesia. Prosthetic plates inserted at surgery for blow-out fracture are said to undergo 'extension' rather than extrusion. Over and above this the standard of proofreading is low and spelling errors are common. Figures 8.10 and 8.12 have their legends exchanged.

All this is rather a pity because where Dr Richards talks about management she is generally quite sound. The sections on sixth nerve palsy, Duane's syndrome and the timing of surgery for congenital esotropia are all clear and to the point. There is a good section on anaesthesia by Dr J T Herbert. The illustrations are generally good although unnecessarily copious. I do not believe that it takes 12 pictures to illustrate a limbal conjunctival incision (Fig 1.5, page 10).

The greatest problem, however, is that the book tries to be at the same time a textbook of strabismus surgery and a manual of 'how to do it,' apparently aimed at someone who has never been in an operating theatre. Nearly an entire chapter is devoted to skin cleaning and draping of the patient prior to surgery. Exhaustive descriptions are given of how to hold a needle and pass it through sclera. The suggested set of instruments for squint surgery includes no fewer than seven muscle hooks.

Finally, there are a number of points on which I would disagree with Dr Richards. I do not think parents should be kept away from the anaesthetic induction area (page 8). In most cases parents and children seem to benefit from staying together until the child is unconscious. In the section on superior oblique tuck (page 42) measurements are given for tuck amounts irrespective of the operative findings and there is no mention of the peroperative traction test popularised by Saunders and used by most surgeons to avoid a disabling secondary Brown's syndrome postoperatively. The useful technique of selective tenotomy at the superior oblique insertion is not mentioned.

In the section on the management of dysthyroid eye disease (page 79) it is suggested that where tethering of medial and inferior recti coexist they should not be dealt with at the same time. I can find no reference to methods of charting fields of diplopia in the follow-up of patients with incomitant squint. On page 138 it is suggested that all scleral sutures that appear to perforate the eye wall should be treated with prophylactic cryotherapy, if necessary by calling in a retinal surgeon to do this. This seems excessive.

In short, despite its evident good intentions, I cannot recommend this book to surgeons in training.

J P LEE

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NOTES

Diabetes 2000

A symposium on screening and treatment of diabetic retinopathy will be held on 6–8 November 1992 in Innsbruck, Tyrol, Austria. Further details: Dr G F Kieselbach, Univ Klinik f Augenheilkunde, A-6020 Innsbruck, Anichstrasse 35, Austria. (Tel: 0512-504-4185/3748; Fax: 0512-504-3722.)

Marfan syndrome

The Second International Syndrome on the Marfan syndrome will be held on 7–9 November 1992 at the Hotel Nikko San Francisco, San Francisco, CA, USA. This symposium will immediately precede the 42nd Annual Meeting of the American Society of Human Genetics. Further details: Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Building, 720 Rutland Avenue, Baltimore, MD 21205, USA. (Tel: (410) 955-2959.)

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Editorial

Ophthalmic manifestations of childhood leukaemia

The treatment of childhood leukaemia stands out as one of the great achievements of modern haematological practice: remission and cure are now commonplace for a disease which was, at one time, uniformly fatal. Unfortunately, many patients still suffer relapses and in these individuals the promise of a permanent cure is less certain. In this issue Ohkoshi and Tsiaras highlight the prognostic importance of ophthalmic involvement in childhood leukaemia. In a 15 year study period 28 of 131 patients treated developed ocular complications and, of these, regrettably only one patient survived. The remaining 27 patients all died within 28 months from the onset of the ophthalmic involvement. All patients with ophthalmic manifestations had either bone marrow relapse or central nervous system involvement and the authors attribute the poor prognosis to these associated factors. Ocular involvement would, therefore, appear to be the harbinger of a relapse rather than its progenitor.

Whilst the authors must be congratulated for a detailed and informative study, some caution must be exercised in interpreting their results. Patient recruitment began in 1972 and it is probable that recent treatment regimens will provide a greater prospect of remission or cure; particularly in cases of relapse following initial therapy. Indeed, repeated modifications of therapeutic regimens used in the treatment of acute lymphoblastic leukaemia have resulted in progressive improvements in patient survival.[1] Recent studies have also reported long lasting second remissions in about one third of children suffering from this condition.[2]

In addition to its primary aim, this article serves to remind the ophthalmologist of the diverse spectrum of the ocular involvement in childhood leukaemia which can, broadly speaking, be divided into three groups: neuro-ophthalmic features associated with central nervous system involvement, vascular abnormalities reflecting changes in haematological status, and direct infiltration of the ocular tissues.

Neuro-ophthalmic signs of central nervous system disease include papilloedema, secondary to raised intracranial pressure, and isolated cranial nerve palsies. Vascular abnormalities typically affect the retina and include intraretinal haemorrhages, cotton wool spots, and venous occlusions.[3] Vitreous haemorrhage may also occur. Infiltration typically affects the optic nerve, anterior segment, and orbit. Whilst optic nerve infiltration is usually related to central nervous system involvement, anterior segment infiltration frequently occurs in the absence of central nervous system disease. Novakovic *et al*[4] recently reported eight cases of anterior segment involvement in acute childhood leukaemia, only two of whom had concurrent central nervous system involvement or bone marrow relapse. This is in sharp contrast to the results of the study reported in this issue. Anterior segment involvement is characterised by either diffuse whitish thickening of the iris or a pseudohypopyon. Any child with leukaemia who develops 'iritis' should be regarded as having a relapse of the leukaemia until proved otherwise[4] and, in such cases, anterior chamber paracentesis or iris biopsy is essential.

Although the ophthalmologist has a secondary role in the treatment of childhood leukaemia, a prompt recognition of the ocular manifestations and their importance as a sign of possible extramedullary disease is crucial if appropriate therapy is to be initiated.

IAN RENNIE

1 The Medical Research Council UKALL trials 1972–84. Improvement in the treatment for children with acute lymphoblastic leukaemia. *Lancet* 1986; i: 408–11.

2 Henze G, Fengler R, Hartmann R, Kornhuber B, Janka-Schaub G, Neithammer D, *et al.* Six-year experience with a comprehensive approach to the treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85). A relapse study of the BFM group. *Blood* 1991; **78**: 1166–72.

3 Schachat AP, Markowitz JA, Guyer DR, Burke PJ, Karp JE, Graham ML. Ophthalmic manifestations of leukemia. *Arch Ophthalmol* 1989; **107**: 697–700.

4 Novakovic P, Kellie SJ, Taylor D. Childhood leukaemia: relapse in the anterior segment of the eye. *Br J Ophthalmol* 1989; **73**: 354–9.

British Journal of Ophthalmology 1992; **76**: 642–645

ORIGINAL ARTICLES

Myopia following penetrating keratoplasty for keratoconus

Stephen J Tuft, Fred W Fitzke, Roger J Buckley

Abstract

The frequent occurrence of spherical myopia after penetrating keratoplasty for keratoconus is partly the result of the excessive dioptric power of the grafted cornea which occurs when the diameter selected for the donor button is greater than the diameter of the host incision. This excessive power could be reduced by eliminating disparity between the diameters of the graft and host. To determine what proportion of the myopia in these eyes would persist as a result of axial myopia the axial lengths of 60 patients grafted for keratoconus and 25 emmetropic controls were compared. A keratometry, objective refraction, and contact probe ultrasonic biometry were performed on all eyes. A comparison of the results with a representational schematic eye indicated that the mean spherical refractive error of the grafted keratoconic eyes (−4·83 dioptres) was the combined effect of steepness of the corneal graft (mean radius of curvature 7·46 mm) and an abnormally great axial length (mean 24·84 mm). The increased axial length was mainly the result of elongation of the posterior segment of the globe with a small contribution from an increased anterior chamber depth. Though axial myopia is common in keratoconus, a further study of 70 keratoconic eyes that had not been grafted showed no statistically significant correlation between the posterior segment length and the severity of corneal ectasia. These data suggest that even if excessive corneal power is eliminated after penetrating keratoplasty for keratoconus the associated axial myopia would still produce a mean spherical refractive error of at least −2·8 dioptres.

(*Br J Ophthalmol* 1992; **76**: 642–645)

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Accepted for publication 21 May 1992

Penetrating keratoplasty is reserved for the minority of patients with keratoconus who cannot attain a satisfactory visual acuity with spectacles or contact lenses. Though a first graft to an eye is usually technically successful in terms of clarity and survival,[1-3] astigmatism and residual myopia may prevent full visual rehabilitation.[3-5] This has prompted interest in the origins of postoperative refractive error and methods for its reduction.[6-8]

A disparity between the shape of the wound margins of the host and recipient is thought to be the primary cause for post-keratoplasty astigmatism,[9-11] but the origin of spherical myopia following keratoplasty for keratoconus is the subject of debate. It has been demonstrated that the use of an oversized donor corneal button produces a steeper graft contour which results in an excessive corneal dioptric power,[6-8,12] but Wilson *et al* observed that grafted keratoconic eyes have a greater postoperative myopic spherical error than eyes grafted for Fuchs' dystrophy, even if the differences between diameters of the host and donor trephines (0·25 mm) are the same in the two groups,[8] and suggested a contribution by factors in addition to the graft contour toward the final refraction. The importance of the axial length of the globe was highlighted by Brooks *et al* who reported that the mean axial length of eyes with keratoconus was greater than emmetropic controls and that there is a correlation between the spherical myopic error following keratoplasty and the axial length of the eye.[5]

To characterise the origin of myopic error associated with keratoplasty for keratoconus we have compared the axial length and keratometry of grafted eyes and emmetropic control eyes. To assess if the grafted eyes could have been rendered emmetropic by eliminating overpower of the cornea we have used a representational schematic eye to determine the contribution of the axial length to the final refraction. To determine if there is a relationship between the severity of corneal disease in keratoconus and an elongation of the rest of the globe we studied the eyes of patients with keratoconus who had not undergone surgery.

Patients and methods

We examined the right eye of 60 phakic patients who had a clear penetrating keratoplasty for keratoconus and who had all sutures removed for at least 6 months. No eye had been grafted more than once. Patients were examined consecutively as they presented for review in clinic, but four eyes that had undergone refractive surgery for astigmatism were excluded from the study. Surgery had been performed by a number of different surgeons, but in the majority of cases the donor button was cut from the endothelial surface with a trephine 0·25 to 0·50 mm larger than the host and secured with a single 10/0 running suture. The follow-up period was defined as the interval between the removal of graft sutures and the observation point. The

Table 1 Clinical details of 60 patients who received a penetrating keratoplasty to their right eye

	Mean	*(Range, 1 SD)*
M:F ratio	1·73:1	
Age at examination	36·6 years	(19–61, 9·37)
Age at onset	20·4 years	(8–38, 6·9)
Follow-up post-ROGS*	6·7 years	(0·5–20, 4·9)
Cylinder (refractive)	4·24 dioptres	(0–19, 3·17)
Cylinder (keratometer)	0·77 mm	(0·02–1·9, 0·46)
Spherical equivalent	−4·83 dioptres	(3·4—19·5, 4·17)
Mean keratometry reading	7·46 mm	(6·2–8·9, 0·46)
Axial length	24·84 mm	(21·7–30·1, 1·64)
Posterior chamber	17·12 mm	(14·7–22·1, 1·52)
Anterior chamber	3·76 mm	(2·8–4·73, 0·42)
Lens thickness	3·96 mm	(3·14–4·78, 0·32)

*Removal of graft sutures.

right eyes of 70 patients with keratoconus who had not had surgery were studied to compare their axial length and severity of their keratoconus. To establish our normal values for biometry and keratometry 25 volunteers were recruited from the hospital staff; they were age and sex matched with the unoperated keratoconus group and all had an unaided Snellen acuity of 6/6.

Keratometry was performed using a Bausch and Lomb keratometer that could be modified to measure high corneal powers. An objective refraction was obtained using a streak retinoscope without cycloplegia, and the axial length was measured along the visual axis using an ultrasonic contact probe (Allergan/Humphrey Biometer 820). Using this technique the anterior chamber depth is defined as the distance between the anterior surface of the cornea and the anterior surface of the lens, the lens thickness is the distance between the anterior and the posterior surfaces of the lens, and the posterior chamber depth is the distance between the posterior surface of the lens and the vitreoretinal interface. We have used the posterior chamber depth as an index of globe length because of the uncontrolled variables in the anterior segment such as corneal ectasia, indentation of the cornea by the contact probe,[13] and alteration of the lens thickness with age and accommodation. We have estimated corneal flattening by the tip of the ultrasonic contact probe by comparing anterior chamber depth measurements from 10 emmetropic right eyes with readings obtained on the same eyes by an optical method (Haag Streit), taking five readings with each method from each eye. For comparison of the groups we have used the *t* test, and for a comparison between readings we have used the paired *t* test.

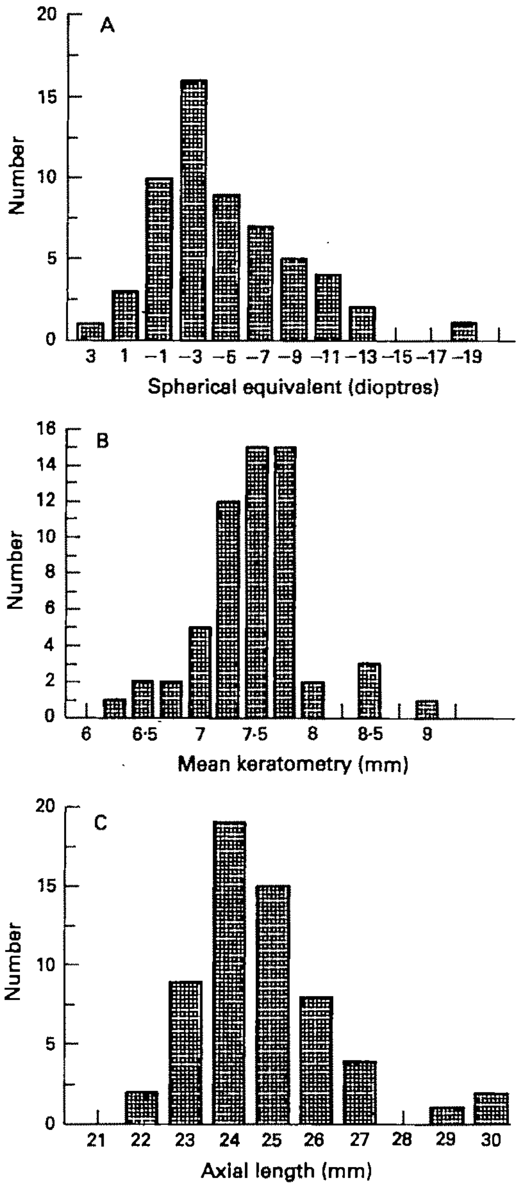

Figure 1 (A) Histogram of the spherical equivalent of the subjective refraction of 60 grafted right eyes following removal of all sutures. Readings are skewed toward myopia (mean −4·83 dioptres, range +3·4 to −19·5). (B) Histogram of the mean corneal keratometry of 60 grafted right eyes. Note that the mean of the keratometry readings (7·46 mm) is significantly steeper than normal (7·80 mm). This leads to an 'overpowered' cornea following surgery. (C) Histogram of the axial length of 60 grafted right eyes measured by A-scan (mean 24·84 mm). There is a skew toward globes with axial lengths greater than normal (23·46 mm in this study). This would tend to produce axial myopia.

A computer model of the optics of the eye was used which emphasised an anatomically correct representation of the optical components and which allowed modification of each of the optical elements.[14,15] The surfaces were represented by aspherical, three-dimensional surfaces and the refractive index distribution was based on measured values from the literature. In particular, the crystalline lens was represented by a combination of graded refractive index changes within each of the major developmental zones along with a step change in refractive index corresponding to the discontinuities visible in slit-lamp images. The retinal surface was represented as aspherical and based on measured values. The parameters of corneal curvature and axial position of the surfaces were modified to incorporate the measured values from this study and the resulting optical effects computed. We have assumed that the refractive indices of the lens components are the same in the three study groups.

Results

All 60 grafted right eyes in this study had a corrected Snellen acuity of 6/9 or better. Contact lenses were the preferred method of visual correction for 55% of patients at the time of observation, 35% wore spectacles, and 10% wore no correction. The characteristics of the 60 patients are presented in Table 1. From the distribution of the spherical equivalents (Fig 1A), it may be seen that there is a skew toward a myopic error and only two eyes were more than 0·25 dioptres hypermetropic. The distribution of the mean keratometric readings (Fig 1B) indicates a skew toward steeper corneas following keratoplasty, with a mean value of 7·46 mm compared with 7·80 for emmetropic control eyes. The distribution of the axial lengths is skewed towards longer eyes (Fig 1C).

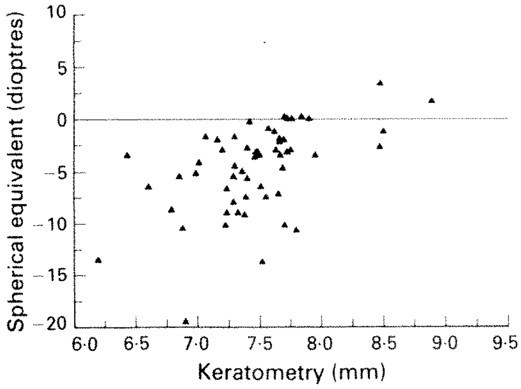

Figure 2 Scatter plot of spherical refraction of 60 grafted right eyes versus their mean keratometry. There is a significant tendency for eyes with steeper corneas to have a greater myopic error.

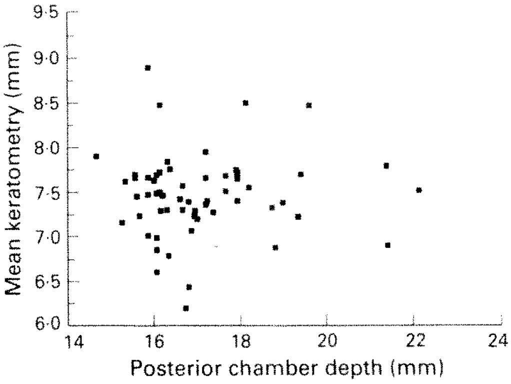

Figure 4 Scatter plot of the mean keratometry of eyes with keratoconus that had not been grafted versus their posterior chamber length. There is no correlation between severity of disease (steepness of the cone) and elongation of the eye.

When we compared the final spherical refraction with the mean keratometry (Fig 2), the posterior chamber depth, or the axial length (Fig 3) there was a positive correlation for keratometry (correlation coefficient 0·529, $p<0·001$) and axial length (correlation coefficient −0·738, $p<0·001$), such that a final myopic error was associated both with steeper corneas and an increased globe length. However, when we compared the posterior chamber depth with the mean keratometry there was no correlation (correlation coefficient 0·0335, $p=0·8$), indicating that steeper corneal grafts did not tend to occur in longer eyes.

A comparison between the mean keratometry and the posterior chamber depth of keratoconus eyes that had not had a penetrating keratoplasty showed no significant correlation (Fig 4) (correlation coefficient 0·0676, $p=0·596$) which suggests that there is not a direct relationship between the severity of keratoconus, as indicated by ectasia of the cornea, and ectasia of the rest of the globe. There was also no statistically significant difference between the axial lengths or posterior chamber depths of the groups of keratoconic eyes that had received a penetrating graft and those that had not (Table 2); however both groups of keratoconic eyes were significantly longer than emmetropic controls ($p<0·001$). We confirmed a significant ($p<0·001$) difference in the measurement for the anterior chamber depth of the normal eye when we compared an optical method (mean 3·57 (SD 0·32) mm) with an ultrasonic contact probe (mean 3·17 (SD 0·29) mm), which would produce low values for axial length measurements with the latter method.

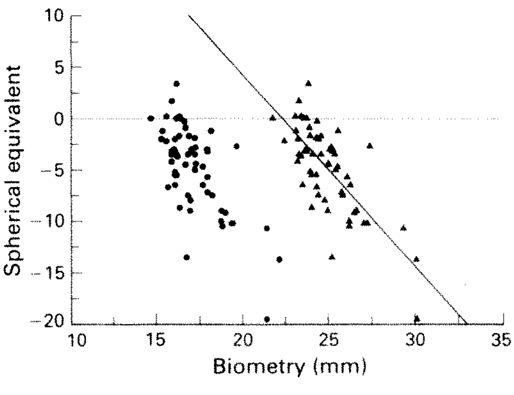

Figure 3 Scatter plots of the spherical equivalent of grafted eyes versus both their posterior chamber depth (circles) and axial length (triangles) measured by A-scan. There is a significant tendency for greater myopia to occur in eye with greater axial lengths ($p=0·001$) and with greater posterior chamber depths ($p=0·001$). These data exclude an effect solely due to corneal ectasia as a result of the steep graft.

The contribution of the difference in the grafted corneal curvature from the normal was calculated to be −1·2 dioptres. The contribution from the increased axial length was −2·8 dioptres using standard values (24·0 mm)[11,15] or −4·6 dioptres using data uncorrected for corneal indentation. In total, these two components were calculated to contribute between −4·0 to −5·8 dioptres of refractive error. The contribution to the final refractive error from axial length was therefore approximately three times that of the corneal curvature contribution. The contribution of lens thickness differences and of the position of the lens relative to the other optical components was calculated to contribute less than 0·1 dioptres each.

Discussion

The objective of penetrating keratoplasty for keratoconus is both to flatten the radius of curvature of the anterior corneal surface and to remove axial corneal scarring. An emmetropic eye is an ideal end-point, but corneal astigmatism and residual spherical myopia usually occur.[4,5,16] Spherical myopia has been attributed to excessive corneal power owing, in part, to the use of an oversize donor button.[6-8,17] The practice of using an oversized button for keratoplasty was

Table 2 Ocular biometry – right eyes

	Number	*Mean*	*SD*
Axial length			
Normals	25	23·46	0·78
Keratoconus – grafted	60	24·84	1·65
Keratoconus – ungrafted	70	24·47	1·65
Comparing normal and grafted eyes with keratoconus, p=<0·001			
Comparing grafted with ungrafted eyes with keratoconus, p=0·2			
Posterior chamber length			
Normals	25	16·42	0·72
Keratoconus – grafted	60	17·12	1·52
Keratoconus – ungrafted	70	17·05	1·52
Comparing normal and grafted eyes with keratoconus, p=<0·005			
Comparing grafted with ungrafted eyes with keratoconus, p=0·7			

introduced to reduce the incidence of wound leaks and aphakic glaucoma in the early postoperative period[18]; however glaucoma is not associated with keratoplasty in phakic patients.[19–23] A 0·2 mm difference between the radius of the donor button and host bed has therefore been recommended to safely minimise wound disparity.[24–26] A further reduction in spherical myopia was reported by Girard *et al* who used a donor button smaller than the recipient.[12]

Although the effect of excessive power of the cornea may have been exaggerated in this series by the use of some donor buttons 0·5 mm larger than the host trephine, our results indicate that the greater proportion of the spherical myopia is the result of an abnormally large axial length. Even by eliminating excessive corneal power approximately 80% of the study group would still be myopic. Unfortunately penetrating keratoplasty reduces the central corneal ectasia of keratoconus but has little effect in reducing the axial length of the globe.

We have considered whether it may be possible to modify the final refraction by altering the relative sizes of the donor and host trephine – for example, attempting to obtain a flatter graft in an eye with a high axial length, but consider that the safety and benefit of using donor buttons cut smaller than the donor trephine is as yet unproved. In practical terms the individual variability of the final corneal contour and the gradual steepening of the cornea in the postoperative period[27] may make it difficult to predict accurately the final refraction. It may also be argued that as long as patients continue to require contact lenses to overcome corneal astigmatism the presence of a coexisting myopia is of little significance.

Finally, it has been established that there is an association between keratoconus and simple myopia, and it has even been suggested that the two conditions may share a common disorder of connective tissue metabolism.[28] However, unlike Brookes *et al*,[5] when we used either keratometry or the need for penetrating keratoplasty as criteria for the severity of keratoconus, we were unable to establish a direct relationship between the length of the posterior segment of keratoconic eyes and the severity of their corneal disease.

Since acceptance of the paper the authors acknowledge the publication of a paper by Lanier *et al* who obtained similar values for axial lengths in keratoconus using applanation ultrasonography. They measured a mean reduction in globe length of 0·91 mm in eyes receiving a penetrating keratoplasty with a donor trephine 0·3 mm smaller than the host.
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Deep lamellar keratoplasty on air with lyophilised tissue

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Abstract

Deep lamellar keratoplasty on air involves injecting air into the corneal stroma to expand it to several times its normal thickness. This method is designed to facilitate dissection of the deep stroma and reduce the risk of perforation of Descemet's membrane when carrying out deep lamellar keratoplasty. We have modified the technique by using prelathed freeze-dried donor tissue and report our results in a series of patients with corneal stromal scarring owing to a variety of corneal problems, namely, keratoconus, pterygium, and herpes zoster ophthalmicus. All patients achieved best corrected postoperative visual acuity of 6/12 or better without problems associated with graft failure or rejection. Histopathological examination of corneal tissue following air injection showed surgical emphysema within the cornea and separation of deep stromal fibres from the underlying Descemet's membrane.

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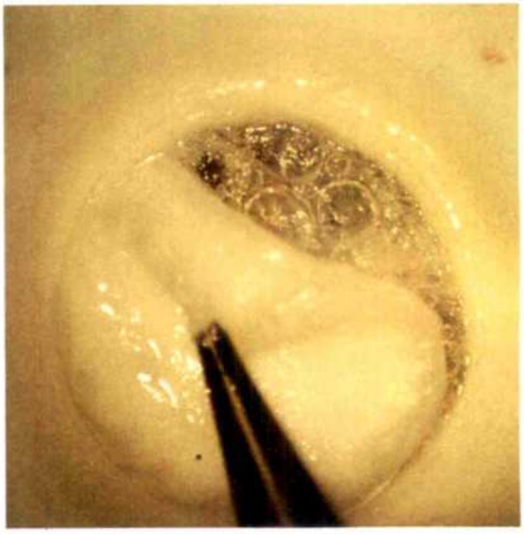

Figure 1 Complete air dissection of the cornea in a cadaver globe. Lamellar dissection is being carried out near Descemet's membrane, and air can be seen in the anterior chamber.

The technique of deep lamellar keratoplasty on air was first reported by Archila in 1985 in a study of patients with a range of corneal disorders where there was central stromal scarring but no endothelial damage.[1] The surgical procedure involves injecting air into the corneal stroma, which then expands and becomes temporarily opaque. The deep stromal fibres become separated from Descemet's membrane and this allows a uniform, deep lamellar dissection to be made which is more clearly visualised because of the temporary opacification of the stroma.

Archila reported using donor corneal tissue of full thickness, whereas Price, in a subsequent study,[2] employed tissue with the endothelium removed. It is recognised that if the endothelium is left on the donor tissue in lamellar keratoplasty it does not survive.[3] Leaving Descemet's membrane intact on the donor tissue is said to give a better optical surface at the interface in lamellar keratoplasty,[4] but histological studies of such grafts show little evidence of healing between the donor Descemet's membrane and underlying stroma, giving reduced wound strength and predisposing to subgraft clefts and even pseudoanterior chambers.[5] Histological examination of the effect of air injection into corneal stroma has also been carried out in animal eyes by Jongebloed *et al.*[6] They performed scanning electron microscopy on sections of porcine corneas which had previously been injected with air and reported the finding of stromal canals.

Lamellar keratoplasty can be used for the treatment of corneal diseases in which the endothelium is healthy, as in keratoconus, some corneal stromal dystrophies, and stromal scarring. However, when compared with penetrating keratoplasty, its advantages must be weighed against its greater technical difficulty, increased operating time, and generally inferior visual outcome.[7] The advantage of lamellar keratoplasty is that it is free from the problems of corneal decompensation owing to poor donor endothelium, since the graft is reliant on the host endothelial cells. It is also recognised that failure of a lamellar graft from rejection is unlikely, whereas in penetrating grafts immunological allograft rejection is the most common cause of late failure.[8] It has been demonstrating that graft epithelium, stromal keratocytes, and endothelium can separately undergo immunological rejection,[9,10] but epithelial rejection is commonly asymptomatic since the graft is resurfaced by host epithelium as the rejection line advances across the corneal surface.[11] In endothelial rejection however, damage to the endothelial cells may compromise the regulation of hydration of the graft, giving bullous keratopathy, since the human endothelium does not replicate readily.[12,13]

In lamellar keratorefractive procedures, such as epikeratophakia, the donor tissue is often freeze-dried as the cellular viability of the tissue is not essential.[14] This simplifies tissue preservation and distribution. In addition, it has been shown that experimental fresh tissue epikeratophakia grafts implanted onto a vascularised bed, in a pre-sensitised recipient, may be rejected, whereas freeze-dried epikeratophakia lenticules are not.[15] The reduced immunogenicity of lyophilised lenticules may be an important factor

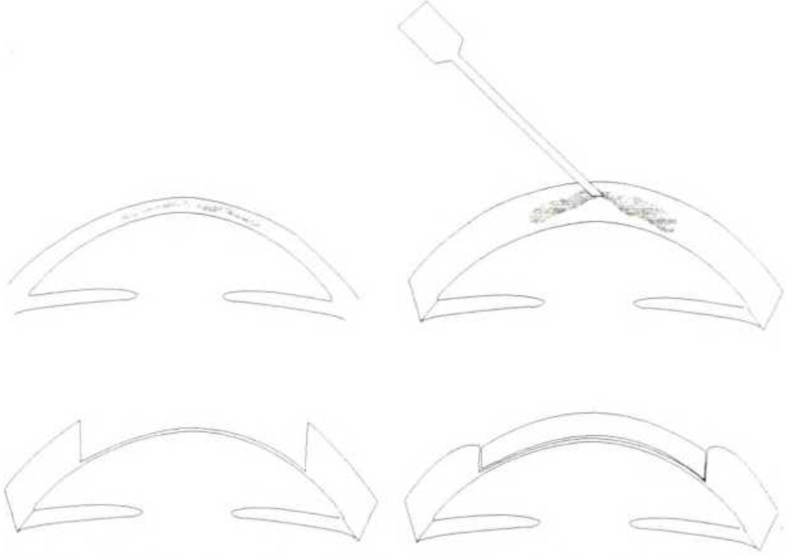

Figure 2 A patient's cornea with central stromal scarring is suitable for this technique. Air is injected and a lamella resected. Lyophilised tissue is sutured in place.

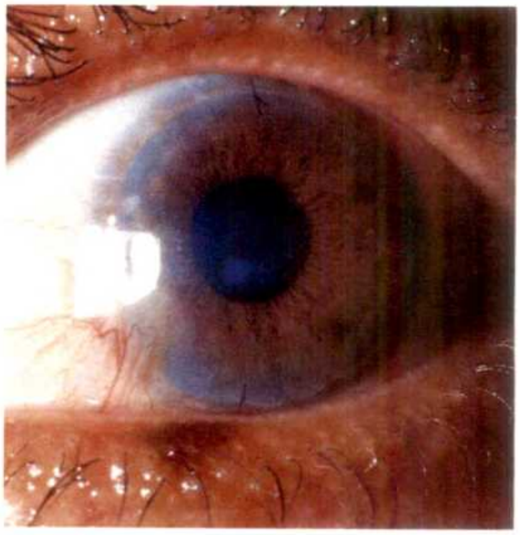

Figure 4 Patient number 2 (pterygium) 6 months postoperatively. The graft used was a 9·5 mm lathed lyophilised lenticule of 100% donor central corneal thickness.

if the recipient patient subsequently were to undergo penetrating keratoplasty since the eye would not be pre-sensitised to donor antigens.

We present our experimental work on human cadaver corneas and the results of using the technique in a series of four patients with different corneal pathologies. The corneal material we used for grafting included both organ-cultured full thickness corneal tissue without endothelium, and lathed lyophilised lenticules.

Materials and methods

IN VITRO WORK

We initially carried out trials in six human cadaver corneas which did not have pre-existing corneal pathology. Two were simply injected with air, and in the others air was injected and experimental lamellar dissection carried out (Fig 1). These eyes were fixed in formalin and then slices were paraffin embedded and sections of 3 μm cut prior to staining with haematoxylin and eosin for assessment by light microscopy.

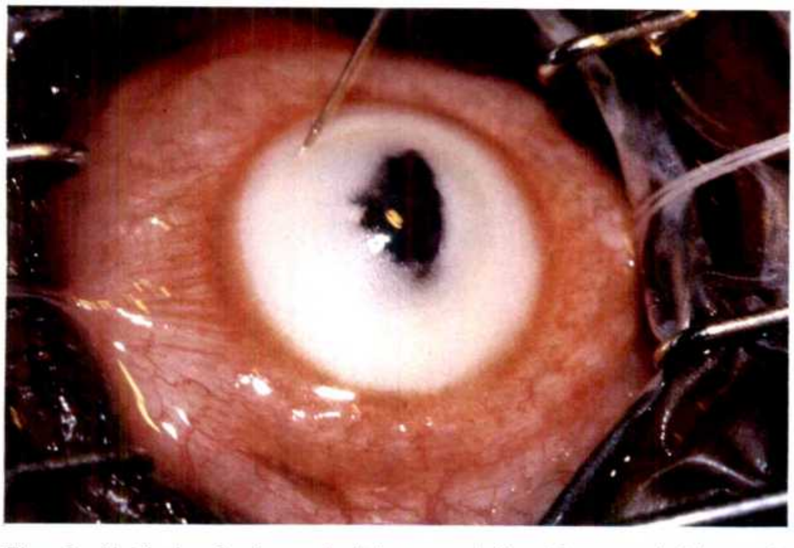

Figure 3 Air injection of patient number 1 (keratoconus). The air has not reached the central zone where there is stromal scarring. Fleischer's ring is highlighted against the opaque insufflated cornea.

CLINICAL SERIES

The four clinical cases selected all had superficial stromal opacities over the visual axis. Two had moderate keratoconus with significant apical scarring rendering them unsuitable for epikeratoplasty, and both were intolerant of contact lenses. The third patient had extensive vascularised subepithelial scarring following herpes zoster ophthalmicus. In this case the corneal new vessels were shut down with an argon laser preoperatively. The remaining patient had a large nasal pterygium with subepithelial scarring extending across the visual axis.

Surgery was performed by one surgeon (CKR) using a method similar to that described by Archila. A 26 gauge needle was inserted obliquely into the stroma in the mid-periphery of the cornea and air was injected until the whole stroma became insufflated if this was possible. Superficial trephination was made and the incision deepened with a diamond knife until Descemet's membrane was approached. Lamellar stromal dissection was carried out using a disposable lamellar blade. Out of the four cases, one patient (number 1) received a tissue-cultured full thickness donor cornea which had its endothelium removed by cellulose sponge. The other three patients received pre-lathed lyophilised lenticules cut to 100% of the donor tissue central corneal thickness (plano lamellar tissue, Keratec Eye Bank, St George's Hospital, London, UK). These lenticules were rehydrated with balanced salt solution just prior to grafting. The grafts were secured with interrupted monofilament sutures (Fig 2).

Results

Though complete insufflation of the cornea by air injection was relatively easy in cadaver eyes, it

Table 1 Patient data

Patient number	*Diagnosis*	*Best corrected pre-op acuity*	*Best corrected post-op acuity*	*Pre-op refraction*	*Post-op refraction*	*Pre-op keratometry*	*Post-op keratometry*	*Comment*
1	Keratoconus	6/18	6/12	N/A	−4·0 Sph −3·5×20°	Irregular <5·5	7·78 at 90° 7·35 at 180°	Fresh tissue graft
2	Pterygium	6/18	6/12	+1·5 Sph −1·75×25°	+2·5 Sph −5·0×155°	Irregular	7·05 at 60° 7·98 at 150°	Epithelial islands at interface
3	Herpes zoster	6/18	6/12	+0·5 Sph +1·0×90°	+1·75 Sph	Irregular	7·69 at 90° 7·66 at 180°	Epithelial islands at interface
4	Keratoconus	CF	6/9	NA	−8·5 Sph +5·0×120°	Irregular <5·5	7·7 at 40° 6·7 at 130°	No complications

was generally incomplete in our clinical cases leaving the area with most stromal scarring or pathology undissected. This occurred at the corneal apex in the keratoconus cases (Fig 3), and in the vascularised peripheral sector of the case of herpes zoster ophthalmicus. Complete air dissection of the cornea was achieved only in the case with the pterygium.

In every case air was found to enter the anterior chamber and, to a varying extent, to track into the subconjunctival tissues. In some instances it was necessary to aspirate the air from the anterior chamber by limbal puncture in order to reduce the intraocular pressure, and it was these problems that prevented complete insufflation of the cornea.

Table 1 shows the results of the clinical cases including the preoperative and postoperative visual acuity, refraction, and keratometric values over the follow-up period of up to 1 year.

The first patient with keratoconus only had a planned 50% lamellar dissection, and postoperatively there was some diffuse interface scarring with a contact lens corrected vision of 6/12. Because the patient was dissatisfied with the visual result he later underwent penetrating keratoplasty.

The second patient who had resection of a nasal pterygium developed small but persistent epithelial defects in the first postoperative month; these healed eventually. Additionally there were three small epithelial islands left at the interface away from the visual axis (Fig 4).

The third patient with vascularised scarring secondary to herpes zoster ophthalmicus had previously undergone extracapsular cataract extraction with posterior chamber lens implantation. Incomplete air dissection was a problem particularly in the area of neovascularisation, and ultimately some deep stromal opacity remained, but this was away from the visual axis.

Patient number four with keratoconus could not be fitted with contact lenses preoperatively; there was obvious central stromal opacity and acuity was counting fingers only. Postoperatively he achieved marked visual improvement to 6/9 with a contact lens. He had no significant complications.

Preoperative spectacle corrected vision ranged between 6/12 and counting fingers. All four patients achieved best corrected vision of 6/12 or better 1 year postoperatively. Considerable postoperative astigmatism was common in the early postoperative phase but tended to settle with time and selective suture removal. Both patients with keratoconus had marked corneal flattening after surgery.

Histopathology

IN VITRO WORK

Figures 5 and 6, stained with haematoxylin and eosin, show sections of human cadaver cornea following air insufflation. Nearly the whole stroma is occupied by small oval holes which are smaller superficially but become larger towards Descemet's membrane. The surgical emphysema of the cornea halts abruptly at the corneoscleral junction adjacent to the trabecular meshwork. The fine stromal structure immediately beneath Bowman's layer appears relatively unaffected, while there is good separation of Descemet's membrane from deep stromal fibres. In no specimen was rupture of Descemet's membrane seen, although the possibility that rupture had occurred in a plane different from that of the sections examined was not excluded.

CLINICAL SPECIMENS

Histological examination of the excised lamellar dissections from the clinical cases revealed a

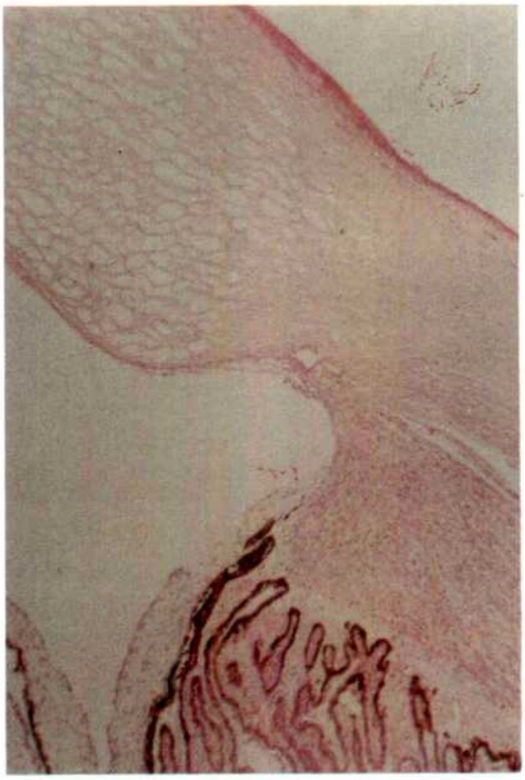

Figure 5 Cadaver cornea following air injection. The stroma is expanded by air spaces which extend only as far as the limbus (haematoxylin and eosin, original magnification × 10).

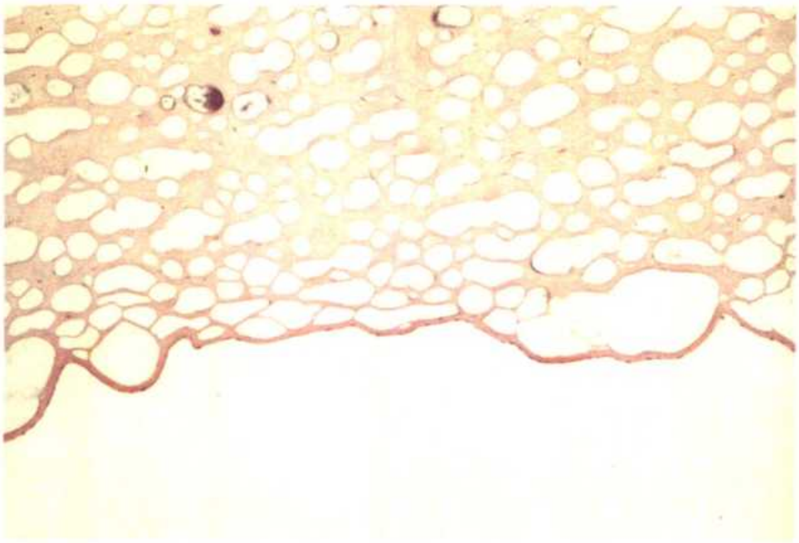

Figure 6 High power view of air dissected cadaver cornea showing separation of Descemet's membrane from deep stromal fibre bundles (haematoxylin and eosin, original magnification ×25).

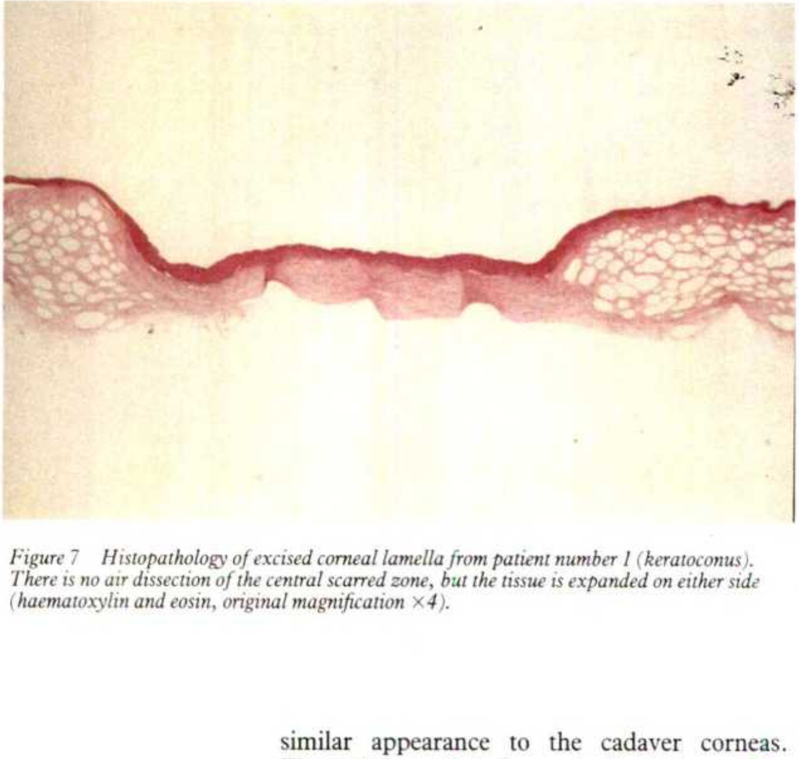

Figure 7 Histopathology of excised corneal lamella from patient number 1 (keratoconus). There is no air dissection of the central scarred zone, but the tissue is expanded on either side (haematoxylin and eosin, original magnification ×4).

similar appearance to the cadaver corneas. Figure 7 shows that air penetration is incomplete in this keratoconus specimen where the central stroma with apical scarring is not inflated by air. Though there is some degree of pre-existing central corneal thinning one can appreciate the marked increase of overall stromal thickness caused by air injection. Our histological sections do not reveal any difference in the epithelial layer overlying injected and non-injected areas, at least under light microscopy.

Discussion

The standard technique for lamellar keratoplasty is to resect the superficial host stroma and to replace the resected tissue with a partial thickness donor lamella. Problems with postoperative interface scarring have caused the technique to be largely discarded in favour of penetrating keratoplasty, which nowadays has a high success rate thanks to modern techniques of endothelial assessment of the donor corneas, and improved tissue handling by microsurgery. Nevertheless it must be remembered that in some conditions – for example, after trauma or ulceration, there may be vascularisation of the recipient cornea, and in these circumstances penetrating keratoplasty is not so successful because rejection problems are more frequently encountered.

Deep lamellar keratoplasty on air provides an enhanced visual contrast of the stroma to be dissected, allowing a more accurate assessment of the depth of incision. This helps to achieve resection of as much deep stroma as possible without perforating Descemet's membrane. In practice, dissection actually at the level of Descemet's membrane still carries a high risk of perforation, either through direct incision through the membrane, or by splitting or tearing of the membrane from indirect forces applied to it.

Because of this risk, in none of our clinical cases did we attempt to resect the full thickness of the recipient stroma, but rather aimed to achieve a near full thickness resection in the central optical zone of the cornea, but a less than full thickness resection in the periphery of the bed where the cornea is thicker. By limiting the near full thickness dissection to the central area alone it was thought that the risk of perforation would be minimised, and Descemet's membrane was not in fact ruptured in any of the clinical cases.

By resecting less than the full thickness of the recipient cornea in the periphery of the graft bed, the risk of perforation by direct downward cutting with the diamond knife is minimised. The resultant graft bed thus has a contour that lies a uniform distance from the original corneal surface. In order to match the shape of this resected bed, the donor tissue used for the latter three patients in the series was pre-lathed to a uniform 100% of the donor tissue's central thickness.

Air dissection was incomplete in each of our patients with stromal scarring, particularly in the area of maximal scarring. It is interesting to note that in cadaver corneas, air dissection is much more easily and quickly achieved than in living tissue, possibly owing to reduced adhesion between adjacent stromal fibre bundles from pre-existing corneal oedema.

We observed air in the anterior chamber in every case, and Price[3] has advocated aspiration with a needle inserted into the anterior chamber to lower the intraocular pressure. In histological sections the air spaces above Descemet's membrane extend extremely close to the trabecular meshwork (which is anatomically continuous with Descemet's membrane). It is, therefore, possible that air gains access to the anterior chamber via the trabecular meshwork. If air had entered the anterior chamber through a rupture in Descemet's membrane one would have expected corneal oedema to be present in this area postoperatively, or the possibility of a 'double anterior chamber' with aqueous tracking into the lamellar graft bed. However neither of these complications was observed in our series suggesting that the air dissection did not rupture Descemet's membrane.

Final spectacle corrected vision in all four patients was better than 6/18 and best corrected vision with a contact lens was 6/12 or better. Whilst these visual results are less good than one would expect with penetrating keratoplasty they must be seen in the light of the reduced risks of lamellar keratoplasty. These include reduced risk of damage to anterior segment structures, the reduction in postoperative steroid treatment, and the lack of immunogenicity of lyophilised lenticules. This technique may thus be the treatment of choice where the aforementioned factors could be anticipated as problems if penetrating keratoplasty were to be undertaken, – for example, in badly vascularised corneas, pre-existing glaucoma or steroid sensitivity, or where there is the likelihood of poor compliance with follow-up.

In summary our experience with deep stromal air injection is that it makes lamellar keratoplasty an easier and safer operation to perform with acceptable visual outcome using either tissue cultured or lyophilised donor material. Further work is needed to improve the surgical technique and define how injected air reaches the anterior chamber, as it would be helpful to avoid this complication. The use of lyophilised tissue should theoretically avoid sensitisation of the eye and this may be beneficial if subsequent penetrating keratoplasty needs to be undertaken.

This paper was presented to the Ophthalmic Section of The Royal Society of Medicine on 13 June 1991.

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Prognostic importance of ophthalmic manifestations in childhood leukaemia

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Abstract

In order to assess the systemic prognosis of children with leukaemic ocular involvement, 63 of 131 patients admitted to hospital with acute leukaemia were evaluated ophthalmically. A total of 28 of 63 showed ophthalmic involvement and were followed up for up to 84 months. Twenty seven of 28 patients (96·4%) died within 28 months after the onset of ocular involvement and within 83 months after the onset of leukaemia. The 5 year survival rate of patients with ophthalmic manifestations was 21·4% (6/28). This survival rate was significantly lower than that of those who lacked ophthalmic manifestations (16/35: 45·7%, $p<0\cdot05$). All of the patients with ophthalmic manifestations had either bone marrow relapse or central nervous system leukaemia. The prognosis was related to risk factors such as central nervous system leukaemia or bone marrow relapse in most cases.

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Though numerous studies[1–8] have shown ocular involvement in leukaemia very few have suggested a relationship between the ocular findings and systemic prognosis.[1 2 4 9 10] In the era before antileukaemic therapy retinopathy was believed to be of no prognostic significance in acute leukaemia.[1 2] Since modern chemotherapy was introduced, it has prolonged the survival period and provided a possibility of cure in acute leukaemic children. Modern chemotherapy, however, has paradoxically increased the incidence of leukaemic cell infiltration especially to the central nervous system. There have been no studies, however, showing a correlation between ophthalmic findings in leukaemia and the systemic course of leukaemia in patients treated with chemotherapy. In this study we investigated the prognosis of patients with ophthalmic findings to see if they played a role in predicting the prognosis of leukaemia.

Materials and methods

From January 1972 to June 1987, 131 children with acute leukaemia were treated and followed at the St Luke's International Hospital (Tokyo) and Juntendo University Hospital. Sixty three of the 131 patients were referred to the department of ophthalmology by paediatricians. Forty seven were referred when signs or symptoms of ocular abnormalities were present and 16 were referred as having risk factors such as central nervous system leukaemia, severe thrombocytopenia, or marked leucocytosis. Twenty eight patients (14 male), showed leukaemic ophthalmic involvement at some point during the course of their disease. Six patients showed ophthalmic involvement at the onset of leukaemia and 22 at the time of either bone marrow or central nervous system relapse. Four patients had isolated ocular leukaemic relapse. The observation period for the 131 children was more than 5 years from the onset of disease for those children who survived. Eighty seven had acute lymphoblastic leukaemia, and 44 had acute non-lymphoblastic leukaemia. In the 28 patients with ophthalmic manifestations, 17 had acute lymphoblastic leukaemia, and 11 had acute non-lymphoblastic leukaemia. The age of the patients ranged from 3 months to 12 years with an average of 6·9 years. The diagnosis of the ophthalmic involvement was made after examination with both direct and indirect ophthalmoscopy and slit-lamp examination.

Among the referred cases 19 patients who had ocular abnormalities which were not directly linked to leukaemia such as infection, side effects of chemotherapy, and/or refractive errors, were excluded. One patient with retinal haemorrhage during remission was excluded because it was felt that a liver disorder was the main cause of the haemorrhage. Two patients with subconjunctival haemorrhage which occurred during remission were also excluded. All patients were treated, according to the protocol of the Tokyo Children's Leukemia Study Group, with multiple chemotherapeutic drugs and in some instances prophylactic irradiation for central nervous system leukaemia. None of the patients had bone marrow transplantation; no patients refused treatment; no patient died from causes other than complications of leukaemia.

In this study, onset of disease was defined as the earliest time that either symptoms or signs were noted; this applied to the underlying leukaemia and to ophthalmic manifestations.

Results

We classified ophthalmic involvements into two major categories: (1) direct leukaemic infiltration

Table 1 Number of the patients with ocular manifestations

	Acute lymphoblastic leukaemia	*Acute non-lymphoblastic leukaemia*
Optic nerve infiltration	5 (5)	0
Uveal infiltration	1 (1)	3 (2)
Orbital infiltration	0	3 (2)
Neuro-ophthalmic sign of central nervous system leukaemia	11 (11)	5 (5)
Retinal haemorrhages and vascular changes	8 (5)	5 (4)
Total	17 (14)	11 (9)

( ) central nervous system leukaemia
Ten had more than two abnormalities

Table 2 Survival of patients with optic nerve infiltration

Type	Ophthalmic findings	Treatment for the eye	*Survival (months)* After ophthalmic manifestation	 After onset of leukaemia	5 year survival
1 Lymphoblastic leukaemia	right eye: severe peripapillary infiltration left eye: moderate swollen disc, seventh nerve palsy	Irradiation, chemotherapy	18 (16)	32	–
2 Lymphoblastic leukaemia	Mild peripapillary infiltration	Irradiation, chemotherapy	22	69	+
3 Lymphoblastic leukaemia	Moderate swollen disc seventh nerve palsy	Not done	16 (5)	60	+
4 Lymphoblastic leukaemia (T cell)	Severe swollen disc third, fourth, sixth nerve palsy	Irradiation not completed	1 (31)	42	–
5 Lymphoblastic leukaemia	Mild swollen disc	Chemotherapy	More than 31	More than 84	+

( ) Survival after nerve palsy

Table 3 Survival of patients with anterior segment leukaemic infiltration

Type	Ophthalmic findings	Treatment for the eye	*Survival (months)* After ocular manifestation	 After onset of leukaemia	5 year survival
6 Monocytic leukaemia	Hypopyon, keratic precipitate, seventh nerve palsy	Chemotherapy	1 (7)	9	–
7 Lymphoblastic leukaemia	Hypopyon, seventh nerve palsy, vitreous and retinal haemorrhage	Chemotherapy	4 (1) (1)	16	–
8 Monocytic leukaemia	Hyphaema, hypopyon, glaucoma	Chemotherapy, irradiation	10	19	–
9 Myeloblastic leukaemia	Keratic precipitate, cells in anterior chamber, retinal haemorrhage, cotton wool spot	Chemotherapy	19 (17)	20	–

( ) Survival after nerve palsy or retinal haemorrhage

Table 4 Survival of patients with orbital leukaemic infiltration

Type	Ophthalmic findings	Treatment for the eye	*Survival (months)* After ocular manifestation	 After onset of leukaemia	5 year survival
10 Myeloblastic leukaemia	Severe proptosis	Irradiation, chemotherapy	15	15	–
11 Myeloblastic leukaemia	Mild proptosis, retinal haemorrhage	Irradiation, chemotherapy	7 (7)	29	–
12 Myeloblastic leukaemia	Mild proptosis	Chemotherapy	10	10	–

( ) Survival after retinal haemorrhage.

(23 cases), and (2) retinal haemorrhages and other vascular changes (13 cases). With direct leukaemic infiltration, four patterns occurred; optic nerve infiltration (five cases), anterior segment uveal infiltration (four cases), orbital infiltration (three cases), and neuro-ophthalmic sign of central nervous system leukaemia (16 cases), which included cranial nerve palsy and papilloedema. The retinal haemorrhages and other vascular changes were the results of haematological disorders. These included retinal or vitreous haemorrhage (11 cases), cotton wool spot (three cases), and tortuous vessels (one case). In the present study, bilateral disc oedema with increased intracranial pressure and no evidence of leukaemic cell infiltration was defined as a neuro-ophthalmic sign of central nervous system leukaemia. Unilateral swelling of the optic nerve head without evidence of elevated intracranial pressure was defined as retrolaminar optic nerve infiltration. The numbers of patients with each type of leukaemia are shown in Table 1. Eleven patients had more than two ophthalmic abnormalities. Direct leukaemic infiltration was treated by systemic chemotherapy and in some instances with intrathecal antileukaemic agents. Irradiation therapy specific to the eye was performed in six patients with leukaemic ophthalmic infiltration. Two patients who had optic nerve infiltration could not receive complete radiation therapy; one patient died during treatment, and the other showed leucoencephalopathy, a side effect of radiation therapy. Among 28 patients with ophthalmic manifestations, 23 (82·1%) experienced central nervous system leukaemia. All of the patients with ophthalmic manifestations experienced either central nervous system leukaemia or bone marrow relapse during the entire course of leukaemia.

Twenty seven (96·4%) of 28 patients died within 28 months from the onset of ophthalmic manifestations and within 83 months from the onset of leukaemia. The survival periods ranged from 15 days to 31 months after the onset of ophthalmic manifestation of leukaemia.

The 5 year survival rate for the 28 patients was 6/28 (21·4%). This was significantly lower than the rate for those who lacked ocular manifestations (16/35, 45·7% $p<0·05$).

Four of five patients with optic nerve

infiltration, died within 22 months and one patient who had moderate optic disc swelling without the evidence of nerve head infiltration is still alive more than 31 months after the onset of ocular involvement (Table 2). The survival periods from the onset of leukaemia ranged from 32 to more than 84 months. The average survival period was 50·8 months.

All of the patients with anterior segment uveal infiltration died within 19 months from the onset of leukaemia (Table 3). The average survival periods were 8·5 months from the onset of ocular manifestation, and 16·0 months from the onset of leukaemia.

All the patients with orbital infiltration died within 15 months from the onset of leukaemia (Table 4). The average survival period of the patients was 18·0 months.

In 16 patients with neuro-ophthalmic signs of central nervous system leukaemia, 11 who had no evidence of infiltration of the optic nerve or other ocular tissues, died within 28 months from the onset of leukaemia (Table 5). Nine patients who developed ocular manifestation with central nervous system recurrence, not as an initial symptom of leukaemia, all died within 7 months from the onset of ocular manifestation. The average survival period of those nine patients was 4·1 months from the onset of ocular manifestation.

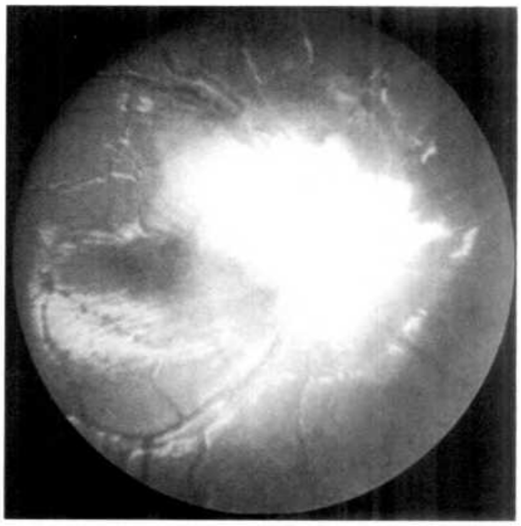

Figure 1 Extensive leukaemic infiltration to the optic nerve head in a patient with acute lymphoblastic leukaemia.

All 13 patients with retinal haemorrhages or other vascular changes died within 17 months of the identification of ocular manifestations. Five of these 13 patients, who presented with retinal haemorrhages or vascular changes alone, died within 12 months of identification of these ocular manifestations (Table 6). Ten of those 13 patients presented with retinal or vitreous haemorrhages at the time of bone marrow relapse not at the time of the initial induction treatment. All of these patients died within 9 months after developing

Table 5 Survival for patients with neuro-ophthalmic sign with central nervous system leukaemia

		Survival (months)		
Type of leukaemia	Ophthalmic findings	After ocular manifestation	After the onset of leukaemia	5 year survival
13 Lymphoblastic leukaemia	Third nerve palsy, papilloedema	2	12	–
14 Erythro-leukaemia	Seventh nerve palsy	4	5	–
15 Myeloblastic leukaemia	Third, seventh nerve palsy	17	17	–
16 Lymphoblastic leukaemia	Seventh nerve palsy	7	20	–
17 Lymphoblastic leukaemia (T cell)	Seventh nerve palsy	5	14	–
18 Lymphoblastic leukaemia	Seventh nerve palsy, papilloedema	2	18	–
19 Lymphoblastic leukaemia	Papilloedema, retinal haemorrhage	7 (7)	83	+
20 Myeloblastic leukaemia	Seventh nerve palsy, papilloedema, tortuous vein	5	50	–
21 Lymphoblastic leukaemia (T cell)	Seventh nerve palsy, retinal haemorrhage	1 (1)	18	–
22 Myeloblastic leukaemia	Seventh nerve palsy, retinal haemorrhage, cotton wool spot	28 (1)	28	–
23 Lymphoblastic leukaemia (pre B cell)	Seventh nerve palsy, macular haemorrhage	4 (1)	14	–

( ) survival period after retinal haemorrhage

Table 6 Survival for patients with retinal haemorrhages or other vascular changes

		Survival (months)		
Type	Ophthalmic findings	After ocular manifestation	After the onset of leukaemia	5 year survival
24 Myeloblastic leukaemia	Vitreous haemorrhage	9	48	–
25 Lymphoblastic leukaemia	Cotton wool spot	12	74	+
26 Lymphoblastic leukaemia	Retinal haemorrhage	0·5	60	+
27 Lymphoblastic leukaemia	Retinal haemorrhage	1	5	–
28 Lymphoblastic leukaemia (T cell)	Massive retinal and preretinal haemorrhage	2	18	–

Table 7 Average survival and standard deviation of patients with ocular manifestations

	Survival (months) (SD)		
	After ophthalmic manifestation	*After onset of of leukaemia*	*5 year survival rate (%)*
Optic nerve infiltration	14·3 (7·9)	50·8 (14·5)	3/5 (60)
Uveal infiltration	8·5 (6·9)	16·0 (4·3)	0/4 (0)
Orbital infiltration	10·6 (3·3)	18·0 (8·0)	0/3 (0)
Neuro-ophthalmic sign of central nervous system leukaemia (without ocular tissue infiltration)	7·4 (7·7)	25·4 (21·3)	1/11 (9·1)
Retinal haemorrhage and other vascular changes alone	4·9 (4·7)	41·0 (25·8)	2/5 (40·0)
Tissue infiltration	9·3 (7·6)	27·3 (20·3)	4/23 (17·4)
Any ocular manifestation	8·5 (7·3)	29·8 (22·1)	6/28 (21·4)

One case who is alive more than 84 months was excluded

these haemorrhages, the average survival period being 3·1 months.

Ten of the 28 patients (35·7%) had decreased vision; three optic nerve infiltration, three anterior uveal infiltration, one orbital infiltration, and three with vitreous, preretinal, or macular haemorrhage. All of these patients died within 1 to 19 months from the onset of visual impairment.

Discussion

Childhood leukaemia, 95% of which is acute, has a better prognosis than adult leukaemia. In children acute lymphoblastic leukaemia accounts for approximately 70% of all cases. With current sophisticated treatment regimens, this form of leukaemia has a cure rate greater than 60%. The predominance of acute lymphoblastic leukaemia in children and its excellent prognosis is the major reason for the difference in survival rate between childhood and adult leukaemia. Many patients, however, still suffer from relapse and are unlikely to achieve a complete cure. The presence of ophthalmic findings in childhood leukaemia is well known. Since modern chemotherapy was introduced, however, very few attempts have been made to relate the prognosis of the disease to ophthalmic manifestations.

In 1976, Ridgway *et al*[4] reported that 80% of children died within 10 months following ocular complications in acute leukaemia. In 1989, Lo Curto *et al*[10] reported that six of 38 patients with leukaemic ophthalmopathy achieved continuing complete remission. These two studies, however, did not indicate the prognosis, because the observation period was short or unclear.

The present study revealed that 96·4% (27/28) of children with acute leukaemia died within 28 months from the onset of ocular manifestations. Accordingly, this suggests that there is very little possibility for leukaemic patients with ocular manifestations to achieve complete cure even with modern treatment methods. One patient, however, is still alive. Lo Curto *et al*[10] reported on the potential of long term complete remission (more than 78 months) in patients with isolated leukaemic ophthalmopathy. These facts may suggest that there is a possibility for patients with ophthalmic involvement to achieve a cure. An aggressive treatment to the eye, therefore, is recommended, not only to protect vision but also to attain a long term remission. We expect that today's more sophisticated treatment may improve the prognosis of patients with ophthalmic manifestations.

The 5 year survival rate for patients with ophthalmic manifestations was lower than for those patients who lacked ocular manifestations. This suggests that the presence of ophthalmic manifestations may be one of the factors which shorten the survival period.

There are two major causes of ocular involvement; tissue infiltration of leukaemic cells and bone marrow dysfunction which causes anaemia and/or thrombocytopenia. In our patients with lymphoblastic leukaemia, most of the ophthalmic tissue infiltration was related to central nervous system leukaemia. Central nervous system involvement is one of the most serious complications which leads to a poor prognosis in acute leukaemia. The period of haematological remission is reduced by central nervous system leukaemia, which is almost inevitably followed by bone marrow relapse.[11] In the present study, 14 of 17 (82·4%) acute lymphoblastic patients with ophthalmic manifestations had central nervous system leukaemia. This incidence was higher than in those who lacked ocular manifestations (9/35:25·7%). The higher incidence of central nervous system leukaemia in patients with ophthalmic manifestations may be one of the factors which shortens the survival period.

Bone marrow dysfunction, on the other hand, is another cause of ophthalmic involvement. This can be seen at the onset of leukaemia but is more prominent at the time of bone marrow relapse. Most patients who had bone marrow relapse experience subsequent relapse and eventually die, even though first remission rate is 85%[12] in acute lymphoblastic leukaemia. Therefore, bone marrow relapse is another factor which shortens the survival period. In the present study, all of the patients with ophthalmic manifestations had either bone marrow relapse or central nervous system leukaemia. Both of these problems, rather than ophthalmic manifestations themselves, we assume, influenced the survival period.

Çavdar *et al*[13] have reported that an ocular manifestation was asssociated with a poor prognosis. They reported that the mean survival rate in patients with acute myeloblastic leukaemic and orbito-ocular granulocytic sarcoma was significantly lower (8·7 months) than in those without orbito-ocular granulocytic sarcoma (28·6 months) after similar treatment. In the present study, the survival periods of the patients with extramedullary infiltration such as anterior segment uveal infiltration or orbital infiltration were extremely low. These facts suggest that extramedullary infiltration other than central nervous system leukaemic cell infiltration may influence the prognosis of acute non-lymphoblastic leukaemia.

Among ophthalmic manifestations, optic nerve infiltration is thought to be a partial presentation of central nervous system leukaemia. Although both optic nerve infiltration and the neuro-ophthalmic sign of central nervous system leukaemia have the same pathogenesis, in our patients these two disorders had quite different prognoses. The average survival period for patients with optic nerve infiltration was 50·8 months from the onset of leukaemia, and 60% of patients survived more than 5 years. In contrast the average survival period for patients with the neuro-ophthalmic signs of central nervous system leukaemia without any other ocular tissue infiltration was 25·4 months from the onset of leukaemia, and the 5 year survival rate was only 9·1% (Table 7). These results suggest that although both processes have the same pathogenesis, neuro-ophthalmic complications may represent a more advanced process, or greater systemic involvement than optic nerve infiltration.

Patients with neuro-ophthalmic signs of central nervous system leukaemia and patients with retinal or vitreous haemorrhages at the time of relapse died within a very short period (average of 4·1 and 3·1 months respectively). These two ocular manifestations, when identified in either central nervous system relapse or bone marrow relapse, suggested a very poor prognosis. The patients who presented with these findings at the time of the initial diagnosis survived longer. This reflects the fact that the remission rate at the time of relapse is lower than the rate at initial induction therapy. This may be related to the tolerance of antileukaemic agents.

This study demonstrated that the presence of ocular involvement with a poor prognostic sign in acute childhood leukaemia. The prognosis, however, was related to risk factors such as central nervous system leukaemia or bone marrow relapse. Some ophthalmic manifestations such as neuro-ophthalmic signs of central nervous system leukaemia, or retinal haemorrhages may be poor prognostic signs if they are seen in the relapse period. Ophthalmic examination in the relapse period, therefore, may be of some value in predicting survival.

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Ultrasound morphology of carotid lesions in retinal ischaemia

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Abstract

The extacranial carotid arteries of 165 patients with retinal ischaemic symptoms were examined with duplex ultrasound. Both the degree of stenosis and the morphological appearance of the lesions were examined. Ipsilateral carotid artery disease was found in 88% of patients. Degrees of stenosis of between 50–99% were found in 33% of patients, the majority of these lesions being complex heterogeneous in nature. Stenosis of <50% was found in 40% of arteries. The majority of lesions causing <20% stenosis were homogeneous in nature. However, in stenosis of 20–49%, 63% of lesions were found to be complex heterogeneous. A similar distribution of lesions was found in the contralateral carotid arteries. It is important to examine both ipsilateral and contralateral arteries, and to evaluate the morphological characteristics of all lesions causing >20% stenosis.

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A relationship between retinal ischaemia and carotid artery disease was first established in 1856, following autopsy findings of carotid artery thrombosis ipsilateral to retinal ischaemia.[1] This relationship has been confirmed subsequently.[2,3]

Diagnostic studies of carotid arterial disease traditionally concentrate on identifying the degree of stenosis caused by atherosclerotic lesions, considering only those which significantly reduce blood flow or perfusion pressure as being potentially clinically important.[4,5]

It has been shown in patients with amaurosis fugax that there is an increased risk of stroke, blindness and early death in those found to have carotid artery lesions causing even less than 50% stenosis compared with those patients with no evidence of carotid disease on ultrasound examination, indicating that retinal and cerebral ischaemic symptoms can be caused by carotid lesions previously considered too small to be of clinical significance.[6] There is evidence that more attention should be given to the ultrasound morphological appearance of atherosclerotic lesions in order to determine their potential clinical significance.[7,8] This factor may be as important in producing symptoms as is the amount of stenosis caused by the disease.

The purpose of this report is to give the results of analysis of carotid arterial lesions examined by duplex ultrasound in 165 patients presenting with symptoms of retinal ischaemia. Both the ipsilateral and contralateral carotid arteries have been examined. The atherosclerotic morphological characteristics and degree of stenosis found have been classified in order to try and identify clinically significant disease.

Material and methods

Between 1985 and 1989, 165 patients (101 male, 64 female, mean age 58 years) were referred to the Diagnostic Blood Flow Laboratory of the Vascular Medicine Unit from an ophthalmic centre for duplex ultrasound examination of the extracranial carotid system. Prior to referral definite retinal ischaemic disease was established on the basis of their ophthalmic assessment, which included funduscopic examination, retinal photography, or fluorescein angiography.

Amaurosis fugax was diagnosed in 79 patients, and 38 patients with permanent unilateral vision loss were found to have central retinal artery occlusion. Branch retinal artery occlusion was found in 48 patients, 17 of whom had partial field defects. Cholesterol emboli were identified in 31 of these patients.

The associated clinical condititions of these patients were: stroke, with a permanent neurological deficit, seven; cerebral transitory ischaemic attack five; peripheral vascular arterial disease 17; ischaemic heart disease 36. In addition, 62 patients were being treated with anti-hypertensive medication and six patients were on medication for control of diabetes mellitus.

An ATL MK5 duplex ultrasound system with a 7·5 MHz imaging facility combined with a 5 MHz Doppler system was used to examine the extracranial carotid arteries. The examinations were recorded on VHS video tape and hard copies made on a Mitsubishi Printer.

The presence or absence of atherosclerotic lesions was established, and where disease was found the degree of stenosis caused was noted together with a description of the morphological appearance of the lesion. This appearance was described as being either homogeneous or heterogeneous.

Homogeneous lesions had an even echo pattern

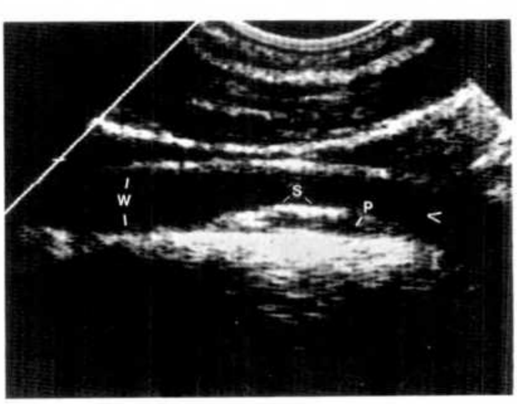

Figure 1 Complex heterogeneous lesion containing a low echo pool (p), without surface irregularity (s). (w) indicates vessel wall and arrowhead direction of blood flow.

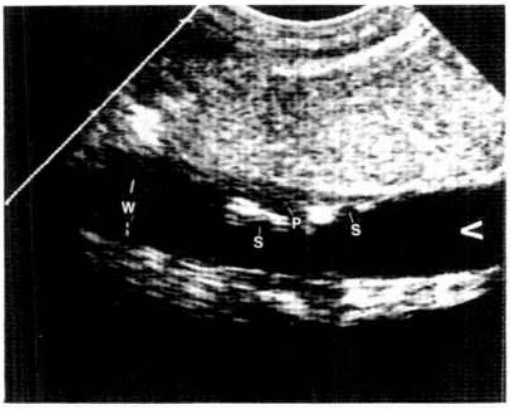

Figure 2 Complex heterogeneous lesion containing low echo pools (p) and having an irregular surface (s). (w) indicates vessel wall and arrowhead direction of blood flow.

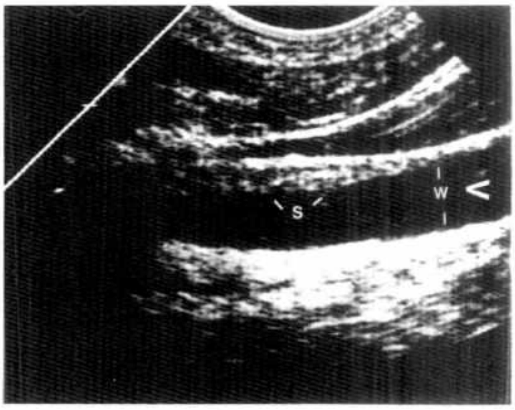

Figure 3 Homogeneous lesion with smooth surface (s). (w) indicates vessel wall and arrowhead direction of blood flow.

throughout the lesion, and heterogeneous lesions had a mixture of low level and high level echo patterns within the lesion (Figs 1, 2, 3). Heterogeneous structures were further subdivided into simple and complex groups. Simple heterogeneous structures had a smooth surface and a more or less equal distribution of low level and high level echoes. Complex structures displayed low echo pools within the lesions and may also have had an irregular or pitted surface at the interface to flowing blood. The carotid arterial atherosclerosis was classified in terms of degree of stenosis caused and by the morphological characterisation of the lesions.

STATISTICAL ANALYSIS

The χ^2 method of statistical analysis was used throughout.

Results

Atheromatous lesions were found to be present in the ipsilateral ateries of 88% of the patients presenting with retinal ischaemia (Table 1). Degrees of stenosis of between 50–99% were found in 33% of patients, and a further 5% of patients presented with total occlusion of the internal carotid artery. Lesions causing less than 50% stenosis were found in 40% of ipsilateral carotid arteries.

The distribution of homogeneous and heterogeneous lesions in ipsilateral and contralateral arteries is shown in Table 2.

There was a significantly greater incidence of heterogeneous than of homogeneous lesions in both ipsilateral and contralateral arteries ($p<0{\cdot}001$). The incidence of complex heterogeneous lesions was significantly greater than simple heterogeneous lesions ($p<0{\cdot}001$); however, there was no difference in incidence of lesions between the ipsilateral and contralateral arteries.

Table 3 shows the relationship between degrees of stenosis and morphological structure. A homogeneous structure was found predominantly in lesions of less than 20% stenosis.

In stenosis of more than 50% all lesions were found to be heterogeneous and of these 82% were complex. In stenoses of 20–49% the majority of lesions were heterogeneous and, of these, 63% were complex in nature.

Discussion

The association between severe carotid artery disease and retinal ischaemic events has been well documented.[2,3]

In this study, the relationship between lesion morphological ultrasound characteristics and patient symptoms was investigated. Lesions were classified as being homogeneous or heterogeneous according to well established criteria.[9,10] Heterogeneous lesions were further subdivided into simple or complex appearances, the latter either containing low echo pools or having an irregular surface pattern. The degree of stenosis caused by the lesion was also established.[11] Image quality and reproducibility are dependent on machine characteristics.[12,13] In this study the same duplex ultrasound system was used for all scans.

A significant number of patients presenting

Table 1 The degree of stenosis in the ipsilateral and contralateral carotid arteries

	Clear	*1–19%*	*20–49%*	*50–99%*	*Total occlusion*
Ipsilateral	38	24	43	57	9
Contralateral	36	35	36	51	1

There is no significant difference in the distribution of lesions between the ipsilateral and contralateral carotid arteries.

Table 2 The morphology of lesions in the ipsilateral and contralateral carotid arteries

	Homogeneous	*Simple heterogeneous*	*Complex heterogeneous*
Ipsilateral	23	23	78
Contralateral	23	34	65

There is a significant difference in distribution between homogeneous and heterogeneous lesions ($p<0{\cdot}001$), and between simple heterogeneous and complex heterogeneous lesions ($p<0{\cdot}001$). However, no difference in lesion distribution was found between the ipsilateral and contralateral arteries.

Table 3 The relationship between lesion morphology and degree of stenosis in the ipsilateral carotid arteries

Degree of stenosis (%)	*Homogeneous*	*Simple heterogeneous*	*Complex heterogeneous*
1–19	18	2	4
20–49	5	11	27
60–99	0	10	47

The majority of lesions causing <20% are homogeneous and those causing >60% stenosis complex heterogeneous. In the 20–49% stenosis group, the majority of lesions are heterogeneous, and of those 63% are complex in nature.

with retinal ischaemia, whose carotid artery disease might not have been considered clinically significant in terms of degree of stenosis, were found to have complex heterogeneous lesions. This suggests that complex heterogeneous lesions may be potential sources of emboli even when occupying less than 50% of the arterial lumen.

Several studies have compared the ultrasound characterisation of atherosclerotic plaques with their histological examination. Homogeneous plaques have been shown to consist of predominantly fibrous material, and have a poor association with symptom production. Heterogeneous plaques have been found to contain either intraplaque haemorrhage or lipid products, and while ultrasound cannot distinguish between these materials, both have been strongly associated with ischaemic symptoms.[7,8,10,12,14-16]

Considerable variation has been reported in the accuracy of ultrasonic diagnosis of ulceration.[12,17-22] However, as it is the acoustic surface of the lesion that is demonstrated by ultrasound, it is more accurate to describe the characteristics of the plaque surface rather than use the term ulceration, which has a specific pathological definition.

Both ulcerative plaques and lesions with surface irregularities have a reported association with ischaemic symptoms.[22,23,24]

In a recent study of 108 patients with suspected carotid atherosclerosis, it was found that it is the heterogeneous nature of the lesion, rather than its size, that is associated with clinical symptoms. Duplex ultrasound of the carotid arteries did not reveal a correlation between degree of stenosis and hemispheric symptoms. However, significant correlation was found between heterogeneous plaques and hemispheric symptoms. The authors noted that the majority of plaques causing >50% stenosis were heterogeneous in nature.[9]

A strong association between complex heterogeneous lesions and retinal ischaemic symptoms has been found in this study. There is a known association between severe stenosis and the production of symptoms, and lesions causing severe stenosis were usually found to be complex and heterogeneous in nature.

In this study of patients presenting with symptomatic retinal ischaemia, 40% of patients were found to have relatively small degrees of stenosis, but quite a high proportion of these smaller lesions were also complex and heterogeneous in structure. This emphasises the clinical importance of the ultrasound morphology of atherosclerotic lesions.

Clinical management of carotid artery disease is still controversial. The recent MRC European Carotid Surgery Trial report indicates benefit from surgery in those patients presenting with 70–99% stenosis, and does not recommend surgery for less than 30% stenosis. The findings for those with stenoses greater than 30% and less than 70% are still awaited.[25] It should be noted that this trial did not take account of lesion morphology.

The role of anti-platelet therapy is widely established, and has been shown to reduce vascular mortality by 15% and non-fatal vascular events by 30% in patients with a history of cerebrovascular or cardiovascular disease.[26]

The non-invasive nature of ultrasound allows investigation of the contralateral asymptomatic arteries. This study shows an unexpectedly similar distribution of severity of lesions in both the ipsilateral and contralateral carotid arteries. There is a trend towards a higher incidence of more severe lesions on the ipsilateral side, a finding which has been observed by two previous reports.[27,28]

A similar morphological pattern of atherosclerotic lesions was also noted on both arterial sides. It has been suggested that the type of carotid disease which gives rise to retinal ischaemic symptoms and that which results in hemispheric transient ischaemic attacks may be different, the former producing small emboli which also cause multiple silent infarcts confirmed by computed tomographic scan, with an associated increased incidence of cerebral atrophy.[29] The similarity of distribution of lesions in the ipsilateral and contralateral sides in this study also raises the possibility that silent cerebral events may be occurring without involving the contralateral retina.

For this reason it is recommended that both carotid vessels be examined routinely as there is a potential danger of emboli from the contralateral side affecting either the retina or causing silent cerebral infarction.

All the patients in this study were referred by an ophthalmic centre specifically for carotid ultrasound studies. The results contain valuable information for the ophthalmic management of these patients. As a result the ophthalmologist may be the first professional to receive information about potential risk not only to the eye but also to the heart and brain.

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Amaurosis fugax in young people

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Abstract

Nine young adults (median age 19·5 years) who suffered from amaurosis fugax (AF) are described. The attacks of AF were short in duration and preceded by premonitory symptoms in five cases and by a migrainous headache in two. In five patients the visual loss progressed in a lacunar pattern unlike the 'curtain' pattern characteristic of AF in older patients. Investigation revealed no evidence of an embolic or atheromatous aetiology. In two cases a minor abnormality was found on echocardiography. We conclude that AF in young adults has a different clinical pattern and may have a different aetiology, possibly migrainous, compared with that seen in older patients. The pattern of visual loss in some of the cases suggests that the choroidal circulation rather than the retinal circulation is primarily affected.
(*Br J Ophthalmol* 1992; **76**: 660–662)

Amaurosis fugax (AF) is defined as transient monocular loss of vision lasting seconds to minutes and is attributed to ischaemia or vascular insufficiency.[1] The impairment progressively may involve the entire visual field; rarely the visual loss lasts for several hours but full recovery of vision occurs. It is usually reported in middle aged and elderly people. A high incidence of ipsilateral carotid atheromatous disease has been found in these patients and fibrin platelet emboli from the carotid or from the heart are thought to be responsible.[2,3] Treatment with aspirin may be effective in preventing further attacks.[4,5] We have seen a group of young patients who reported a similar symptom; we define the clinical features of AF in young people and speculate on its pathophysiology.

Patients and methods

Nine patients presenting to the ophthalmic casualty department with AF were studied prospectively. The median age at onset was 19·5 years, range 11–30 years. There were six males and three females in the group and the average duration of follow up was 2·8 years.

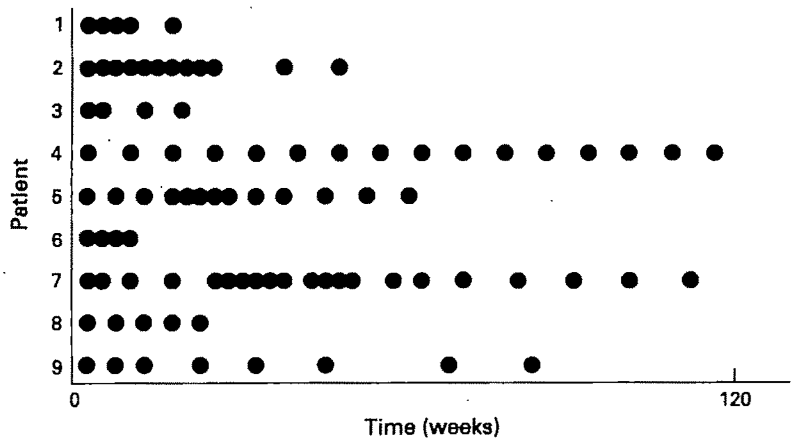

Figure 1 Frequency of attacks of amaurosis fugax in young people.

HISTORY

The relevant features of the clinical history are summarised in Table 1. The history of AF described was quite distinct. The duration of AF was short; the median duration was 5·2 minutes (range 1–30 minutes). Five patients reported premonitory symptoms; these were tingling, numbness, or pain around the eye subsequently affected and preceded the AF by 2 minutes on average (range 30 seconds–15 minutes). In two cases the patients reported a typical migrainous headache preceding the AF.

The median number of attacks was 10·5 (range 4–21). The attacks occurred in clusters over days or weeks in seven of the nine patients and then faded in frequency (see Fig 1). In two cases the attacks occurred at regular intervals.

The pattern of visual loss described by five of the patients was quite different from the classic 'curtain' effect reported in older patients with AF. These patients reported that the vision was lost in a series of 'blobs' or lacunae throughout the field of vision which gradually coalesced into a complete loss of field. After a few minutes the vision returned in a reverse pattern with patches of vision eventually enlarging to a full field (see Figs 2–5). In the other four patients, three reported a non-specific blurring of the field of vision whilst one gave a history of a curtain effect.

As well as the migrainous headaches which preceded the AF in two patients, four other patients complained of migraine headaches at other times and eight of the nine patients gave a family history of migraine.

CLINICAL EXAMINATION

It was not possible to examine the patients during the attacks of AF. In four cases, relatives observed the patient during the attacks and noticed pupil dilatation in the affected eye. This resolved as the vision returned.

On clinical examination the positive findings were:

(1) A systolic murmur consistent with tricuspid and pulmonary regurgitation in a 14-year-old boy who had Crouzon's disease.

(2) Fundus changes in the affected eye consistent with inactive presumed ocular histoplasmosis syndrome in a 30-year-old woman.

(3) Bruits over both carotid arteries in a 14-year-old boy which on Doppler ultrasound were attributed to high flow, consistent with the patient's age.

No other patient had a carotid bruit, irregular

Table 1 *Clinical features of nine cases of early onset amaurosis fugax*

No	*Sex*	*Age at onset*	*Number of attacks*	*Duration (min)*	*Prodrome*	*Pattern*	*Pupil dilated*
1	M	28	5	2–5	Yes	Cluster	Yes
2	M	15	12	1–5	No	Cluster	No
3	F	19	4	3	Yes	Cluster	Yes
4	F	30	16	30	No	Monthly	No
5	M	11	13	1	No	Cluster	No
6	M	22	4	3	No	Cluster	No
7	F	14	21	7	Yes	Cluster	Yes
8	M	19	5	2	Yes	Regular	Yes
9	M	20	8	4	Yes	Cluster	No

Table 2 *Investigations of young patients with amaurosis fugax*

Patient	*Echocardiogram*	*Doppler ultrasound of carotid vessels*
1	patent foramen ovale	normal
2	normal	normal
3	normal	normal
4	normal	normal
5	normal	normal
6	normal	normal
7	pulmonary and tricuspid regurgitation	normal
8	normal	high flow (normal for age)
9	normal	normal

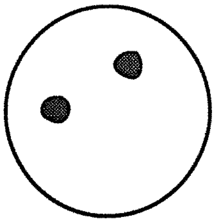

Figure 2 *Pattern of visual loss in some patients with amaurosis fugax. Early lacunae.*

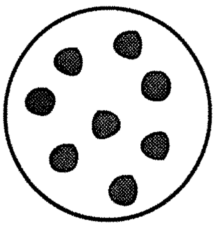

Figure 3 *Extension of lacunae.*

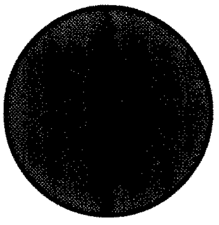

Figure 4 *Complete monocular visual loss.*

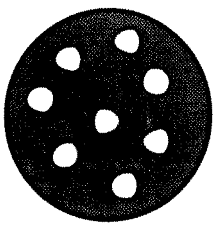

Figure 5 *Lacunar pattern of recovery of visual field.*

pulse, or other clinical cardiovascular abnormality. No retinal emboli or infarctions were seen in any of the patients. The rest of the ocular examination including tonometry and funduscopy was normal. Visual field testing and examination of the nervous system were also normal in all cases.

INVESTIGATIONS

All patients had a normal full blood count, erythrocyte sedimentation rate, urea and electrolytes, serum glucose, and fasting lipids. Anti-cardiolipin antibodies were not detected in the five patients who were tested.

Doppler ultrasound of the carotid vessels and echocardiograms were performed in all cases. The results are summarised in Table 2. The only abnormal findings were on two of the echocardiograms. The 14-year-old boy who had a systolic murmur was confirmed to have pulmonary and tricuspid incompetence. A 28-year-old male patient who had no detectable clinical abnormality was found to have a patent foramen ovale on echocardiography.

Outcome

The median follow-up time of this group was 2·8 years (range 0·5–3·7). In seven of the nine cases the natural history was that of clusters of attacks over weeks to months which then faded out spontaneously. In the remaining two patients the attacks occurred more regularly either monthly or bimonthly and have persisted. No patient has suffered permanent loss of visual acuity, visual field, or any other neurological deficit.

Low dose aspirin was prescribed as therapy in five cases but appeared to have no effect on the clinical course. One woman who had regular repetitive attacks accompanied by migrainous headaches was treated with pizotifen which brought incomplete relief of her symptoms.

Discussion

Sudden transient loss of vision in young patients is relatively rare. There have been previous reports of small numbers of patients whose median ages were in the mid-20s.[6 7] Our patients were younger and included two children under 14 years who gave clear accounts of visual loss.

The history elicited from five of our patients was quite distinct from that typically reported by older patients with AF. The characteristic sequence of a 'curtain' dropping over the vision was found in only one of our cases. Furthermore we did not find retinal emboli or infarcts in any of our patients and there was no evidence of atheromatous carotid disease. The patients we treated with aspirin reported no change in their symptoms and none of the group have subsequently suffered neurological or cardiac events. The absence of these findings suggested that the cause of AF in our group of patients was not carotid or cardiac thromboembolism.

There is some clinical evidence to suggest that AF in young people may be migrainous in origin.[8 9 10] Appelton *et al* call this variant of migraine where visual loss occurs without headache 'acephalgic migraine' and suggest that it has a benign prognosis in young patients.[11] This study provides further evidence to support this hypothesis. Migraine is often a familial disorder,[12] and eight out of nine of our patients had a personal or family history of migraine. The episodes of AF were preceded by sensory premonitory symptoms in five cases, which could have been due to ischaemia from vasospasm in the territory supplied by the ophthalmic artery. The pupillary dilatation reported to us, which occurred during the attack of AF may imply involvement of the ciliary ganglion circulation in the migrainous process and has previously been reported in attacks of migraine.[13] Furthermore the cluster pattern of attacks is a feature of other migrainous disorders such as cluster headaches.[14]

Patients with migraine have been reported to suffer from central retinal artery occlusion and ischaemic optic neuropathy.[15 16] However the pattern of visual loss reported in five of our patients is best explained by a process affecting the choroidal circulation. Conner has previously reported on pigmentary changes in the fundus following migraine attacks and has suggested that the choroidal as well as the retinal circulation can be affected.[17] The lacunar or 'blob' pattern of visual loss described by some of our patients may correspond to the lobular arrangement of the blood supply in the choriocapillaris.[18 19]

The choroidal circulation of primates has a very high blood flow[20] and it is estimated that 70% of blood in the globe is within the choriocapillaris.[21] The blood vessels of the choroid in primates have a plentiful sympathetic and parasympathetic nerve supply.[22 23]

Many of the features of migraine can be explained by vasospastic events.[24] Stimulation of the sympathetic nervous supply to the choroid, which would occur during a migrainous attack, caused a 60% reduction in flow in cats.[25] Reduced blood flow through the choriocapillaris would account for visual loss, so the potential mechanism for choroidal migraine exists.

Previous reports[26,27] indicated that mitral valve prolapse in young patients may be responsible for the symptom of AF, though we were unable to confirm this link. However it is worth noting that patients with mitral valve prolapse have a high incidence of migraine.[28,29]

In summary, we report on nine young patients with AF who in contrast to older patients with AF do not have carotid vessel disease. There is no indication for carotid angiography in the investigation of these patients. We present suggestive evidence that their symptoms may be migrainous in origin and we propose that the choroidal as well as the retinal circulation can be affected in migraine. The natural history of AF in young patients is benign and clusters of attacks tend to resolve completely.

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Endoscopic visualisation of the human nasolacrimal system: an experimental study

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Abstract

Orthograde and retrograde endoscopy of the upper and lower nasolacrimal system was performed using two prototype ultrathin (0·5 mm and 1·1 mm diameter) fibrescopes on four cadaver heads. Appearances were verified by subsequent dissection. The procedure, which we term 'dacryocystoscopy' is described. With modifications this technique may have clinical applications in the treatment of nasolacrimal disorders.

(*Br J Ophthalmol* 1992; **76**: 663–667)

Thorpe[1] was the first to describe the ophthalmic application of an endoscope in 1934 for the removal of intravitreal non-magnetic foreign bodies. With the advent of fibreoptics, flexible and fine calibre endoscopes could be designed and Norris[2-4] adapted a 1·7 mm fibreoptic endoscope for both intraocular and orbital surgery. More recently a new generation of electronic videoendoscopes has become commercially available for gastrointestinal endoscopy.[5] Instead of fibreoptics these endoscopes are based on a charge-coupling device (CCD). The image from the tip of the endoscope is focused on a CCD that transmits the image electronically via a video system to the television monitor. As the image is stored digitally this offers potential capability of image enhancement and computer analysis. A new ophthalmic electronic videoendoscope system for intraocular surgery with a 20 gauge (0·89 mm diameter) probe has been designed.[6] This helps to visualise the pars plana, ciliary body, and the posterior surface of the iris.

Endoscopy of the nasolacrimal system has been reported previously with rigid and semirigid endoscopes.[7,8] Ashenhurst and Hurwitz[8] developed a prototype lacrimal endoscope (canaliculoscope) and used it to visualise the canaliculus and lacrimal sac. Following a recent report[9] on salivary gland endoscopy using 0·8 mm ultrafine diameter fibrescope (endoscope based on fibreoptics) we decided to investigate the feasibility of endoscopic visualisation of the entire nasolacrimal system using prototype fibrescopes on cadavers and to confirm the appearances by dissection.

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Material and methods

Four embalmed cadaveric heads were made available at the Department of Anatomy, Queen Mary and Westfield College. The upper nasolacrimal system was studied in two specimens. To study the lower system (lacrimal sac and nasolacrimal duct) sagittal sections of the head (two) were used. The nasal septum and the inferior turbinate were removed to visualise the opening of the nasolacrimal duct into the inferior meatus.

Two prototype ultrathin fibrescopes PF-5 and XTUF-11 (Olympus Co Ltd, Tokyo) were used. The PF-5 fibrescope has an outer diameter of 0·5 mm, is forward viewing, with a depth of field of 3 to 50 mm (Fig 1). The XTUF-11 fibrescope has an outer diameter of 1·1 mm and has an instrument channel 0·1 mm wide. The depth of field is similar to the PF-5 fibrescope. Both instruments have a 60 degree field of view. CLV-10 OES was used as the light source. The fibrescope was attached to a compact colour video camera (Olympus OTV-F2) which measures 17 mm × 48 mm and weighs 20 g. This produces high resolution images even in low light conditions. This was coupled to a portable CCTV unit (Olympus PVS-1) combining a 9 inch monitor and Video8 VTR; this provided a display of the magnified images during the length of the procedure. The magnification from the fibrescope to the PVS-1 monitor is by a factor of 1·7. A continuous recording was made and at the end of each procedure the tapes were analysed and selected images were printed.

UPPER NASOLACRIMAL SYSTEM (ORTHOGRADE ENDOSCOPY)

After dilatation of the punctum, graduated silver probes ('0' to '3' John Weiss) were inserted to dilate the upper canaliculus. After flushing the nasolacrimal system with normal saline using a syringing canula, healon was injected to keep the structures dilated so as to facilitate introduction

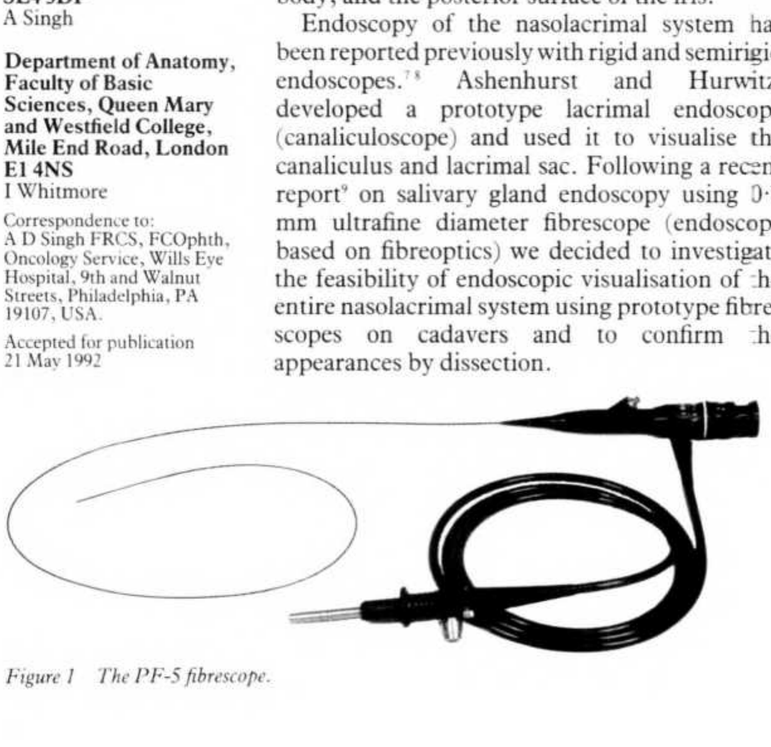


Figure 1 The PF-5 fibrescope.

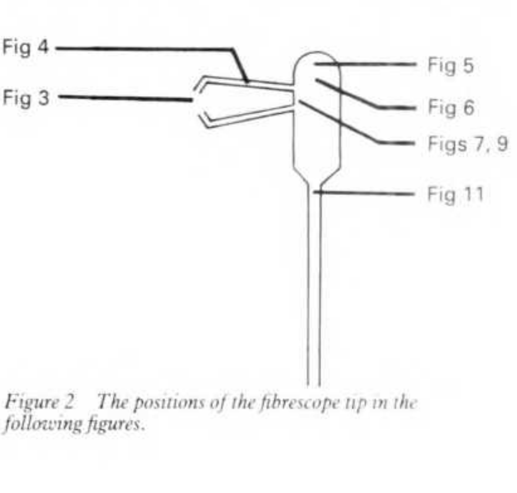


Figure 2 The positions of the fibrescope tip in the following figures.

of the fibrescopes. The PF-5 fibrescope could be introduced easily into the canaliculus up to the level of the lacrimal sac. Greater dilatation with a size '3' silver probe was required before the thicker XTUF-11 fibrescope could be introduced. Neither of the fibrescopes could be manipulated to enter the upper opening of the nasolacrimal duct owing to the rigidity of the embalmed cadaveric tissues and extreme flexibility of the fibrescopes. Both fibrescopes provided adequate visualisation of the upper nasolacrimal system.

LOWER NASOLACRIMAL SYSTEM (RETROGRADE ENDOSCOPY)

Using the sagittal sections of the head and after removing the inferior turbinate, the lower nasolacrimal duct opening was identified by syringing through the canaliculus. Through the lower opening the nasolacrimal duct was gently probed before the fibrescopes were introduced. Again both types of fibrescopes could be passed easily through the nasolacrimal duct into the sac up to the level of the fundus of the lacrimal sac. Both fibrescopes provided good quality pictures allowing us to identify distinctly various structures. A small piece of steel wire (0·1 mm diameter) with a gentle curve introduced into the 0·1 mm instrument channel of the XTUF-11 fibrescope gave it sufficient rigidity and curvature which facilitated exploration and visualisation of the inner aspect of the lacrimal sac. Following visualisation the lacrimal sac was dissected to reveal the features of its inner surface.

Results

Both prototype ultrathin fibrescopes PF-5 and XTUF-11 provided good quality magnified images which could be viewed constantly on the TV monitor and recorded simultaneously.

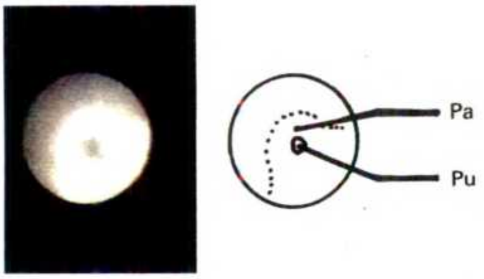


Fig 3a *Fig 3b*

Figure 3 (a) Appearance of the puncta just before insertion of the fibrescope. (b) Pa=papilla and Pu=punctum.

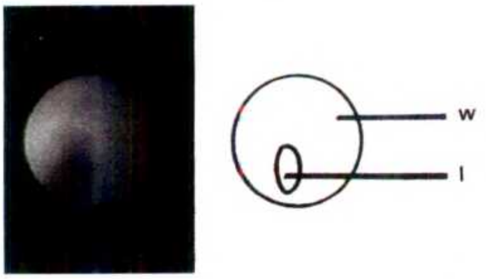


Fig 4a *Fig 4b*

Figure 4 (a) Endoscopic view of the canaliculus. (b) w=wall and l=lumen.

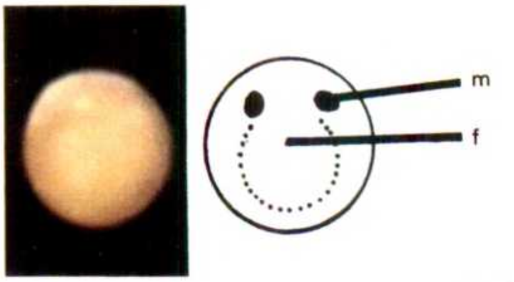


Fig 5a *Fig 5b*

Figure 5 (a) Endoscopic view of the fundus of the lacrimal sac. (b) m=mucosal fold and f=fundus.

Fibrescope PF-5 provided superior quality images (Figs 5, 6, 9) to the fibrescope XTUF-11 (Figs 3, 4, 7). There was no other difference in the optical aspects of the image. The magnification is inversely proportional to the distance beween the tip of the fibrescope and the object to be viewed. The image is further magnified 1·7× between the fibrescope and PVS-1 monitor.

The endoscopic findings are reported for each nasolacrimal structure separately. Figure 2 shows the various positions of the fibrescope tip in the nasolacrimal system in relation to Figures 3–11.

PUNCTUM (FIG 3)

Though this is strictly not an endoscopic picture it is included for the sake of completion. The papilla appeared as a ring of bright light which is surmounted by a dark appearing puncta (post dilatation).

CANALICULUS (FIG 4)

The 'tunnelling' effect is obvious. The canaliculus appeared as a dark hole. The obliquity of the fibrescope tip in relation to the canalicular wall gave it a sloping appearance and this also explains

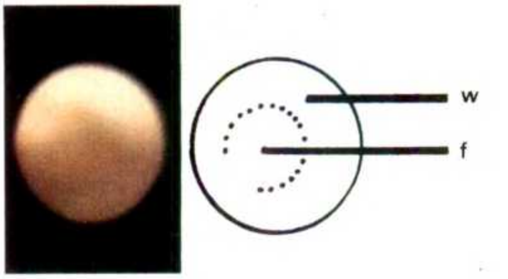


Fig 6a *Fig 6b*

Figure 6 (a) Endoscopic view of the side walls of the sac. (b) w=wall and f=fundus.

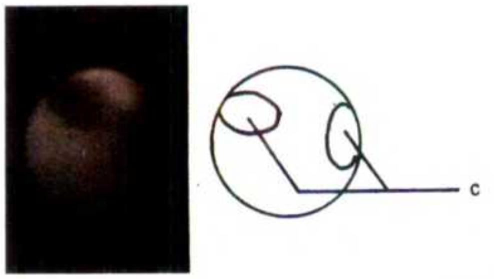


Fig 7a *Fig 7b*

Figure 7 (a) The opening of the canaliculi into the lacrimal sac. (b) c=canalicular openings.

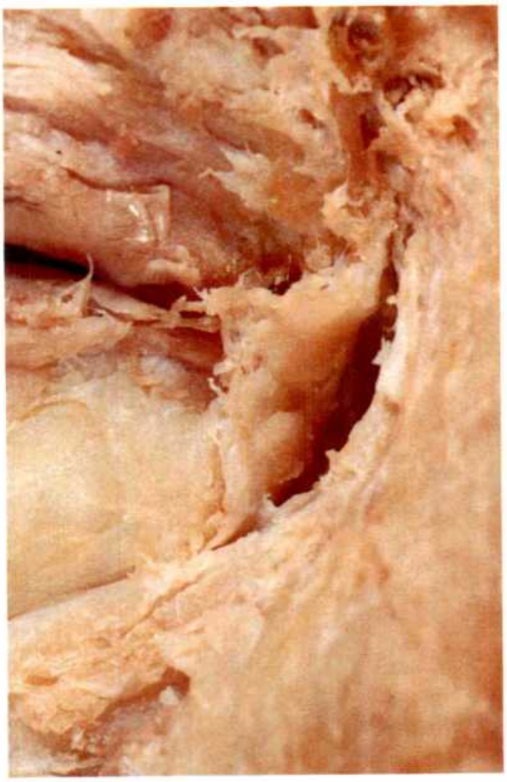


Fig 8a

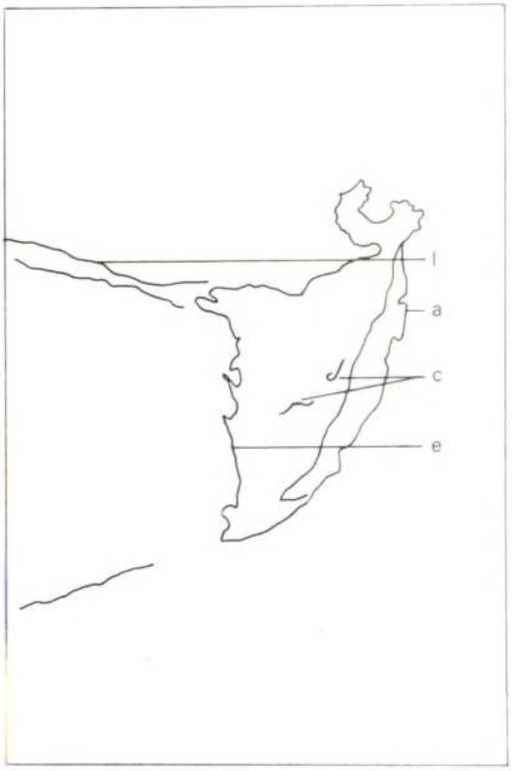


Fig 8b

Figure 8 (a) Appearance after dissection confirms separate openings of upper and lower canaliculi into the lacrimal sac. (b) l=lid margin, a=anterior lacrimal crest, c=canalicular openings, and e=edge of the reflected anterior wall of the lacrimal sac.

the apparent eccentric location of the canalicular lumen.

LACRIMAL SAC (A) (FIG 5)

In this position the tip is very close to the fundus of the lacrimal sac. The central circular brighter zone corresponds to the inner concavity of the fundus. The two bright spots probably represent mucosal folds.

LACRIMAL SAC (B) (FIG 6)

As the tip was withdrawn slightly the appearance changed completely. The central brighter zone was replaced by a central dark zone surrounded by a bright area. This was more obvious in the upper half of the picture. As the tip moved away from the fundus the light being reflected by it reduced (and hence the bright to dark transition) and the light reflected from the side walls of the sac came into the view (outer bright area).

LACRIMAL SAC (C) (FIG 7 AND FIG 9)

With gentle manipulation of the tip it was possible to visualise the inner openings of the canaliculi. The upper and lower canaliculi opened separately into the lacrimal sac in both cases. On subsequent dissection this appearance was clearly confirmed in one case (Fig 8). However in the other case dissection presented an appearance of partial separation (Fig 10).

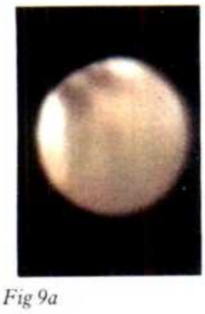


Fig 9a

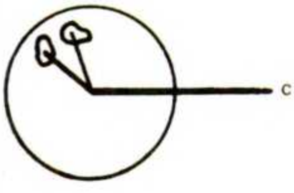


Fig 9b

Figure 9 (a) The opening of canaliculi into the lacrimal sac. (b) c=canalicular openings.

NASOLACRIMAL DUCT (FIG 11)

An oval appearance of the upper end of nasolacrimal duct was identified. The bright spot near the opening is either an artefact or a mucosal fold.

Discussion

The two prototype fibrescopes PF-5 and XTUF-11 investigated in this study provided clear and reproducible images of the entire nasolacrimal system. Our findings demonstrate progress from previous attempts at endoscopic visualisation to include orthograde and retrograde endoscopy. This has enabled the visualisation of the inner openings of the canaliculi and of the nasolacrimal duct origin. In addition endoscopic appearances have been confirmed by dissection.

The fibrescopes used were thinner than the silicon tubing (1·19 mm) suggested by Crawford[10] for intubation of the lacrimal system. The outer diameters of the fibrescopes are compared with the size of silver probes (Fig 12). The fine calibre of these fibrescopes makes them inherently flexible. Because of this the fibrescopes could not be passed into the upper nasolacrimal opening during orthograde endoscopy and the inferior turbinate had to be removed to facilitate retrograde endoscopy. Though the quality of images generated by the fibrescope XTUF-11 were inferior to those of fibrescope PF-5, it may still be the preferred endoscope for two reasons. Firstly, greater thickness (1·1 mm compared

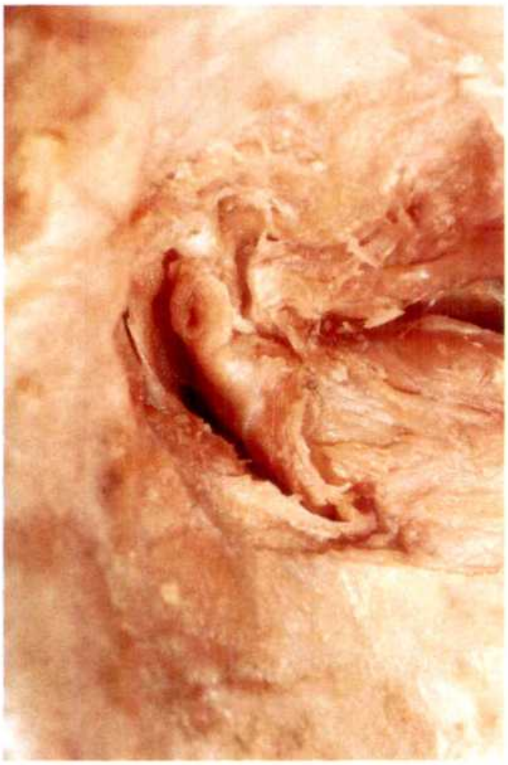


Fig 10a

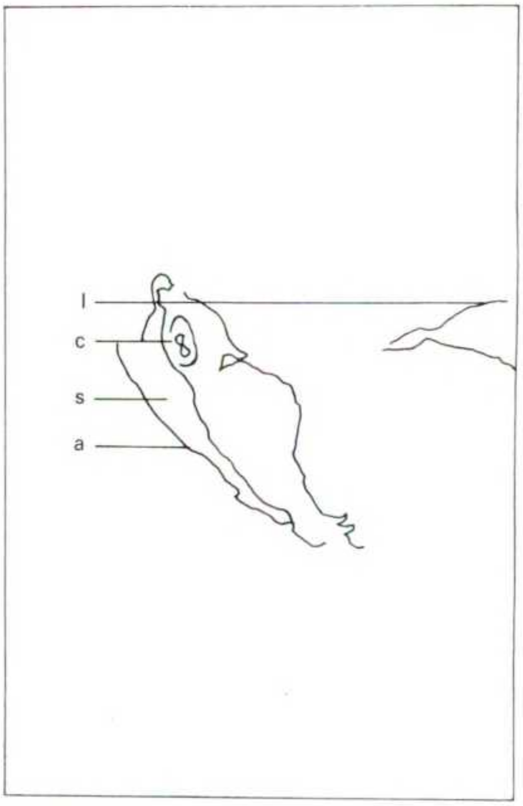


Fig 10b

Figure 10 (a) Partial separation of canalicular openings as seen on dissection. (b) l=lid margin, c=canalicular opening, s=sac lumen, and a=anterior lacrimal crest.

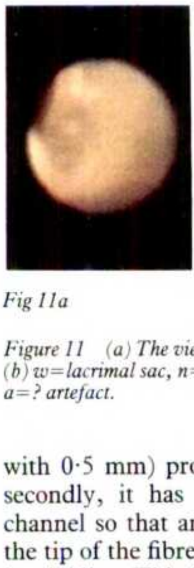


Fig 11a

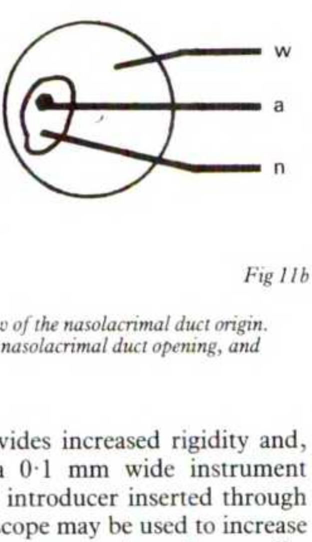


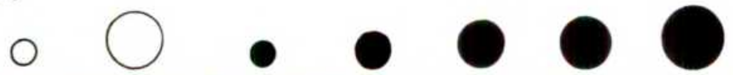
Fig 11b

Figure 11 (a) The view of the nasolacrimal duct origin. (b) w=lacrimal sac, n=nasolacrimal duct opening, and a=? artefact.

with 0·5 mm) provides increased rigidity and, secondly, it has a 0·1 mm wide instrument channel so that an introducer inserted through the tip of the fibrescope may be used to increase its rigidity. This instrument channel may offer interventional possibilities using a suitably designed laser probe. Under direct observation it may be possible to 'cut' through a block in the nasolacrimal duct. A high powered argon laser coupled to a 300 μm quartz fibreoptic has been used to create an intranasal dacryocystorhinostomy fistula in a patient undergoing endonasal laser dacryocystorhinostomy.[11] This is claimed to provide good haemostasis with reduced morbidity. Gonnering *et al*[12] have reported excellent results in 18 patients undergoing transnasal laser assisted lacrimal procedures. They performed laser rhinostomy with carbon dioxide and potassium titanyl phosphate laser delivered through a 300–600 μm fibre under video endoscopic visualisation. In addition chromium-sensitised, and thulium and holmium doped YAG laser (THC:YAG laser) coupled to a 480 μm optic probe can successfully create a limbal sclerostomy.[13] The technique of probing used in children with epiphora is a 'blind' procedure. Bends in the course of the lower tear duct have been shown[14] to exist and canalicular stenosis following probing for congenital nasolacrimal duct obstruction is a well known complication.[15] Using the technique described by us, the upper nasolacrimal duct opening may be visualised and the block in the lower nasolacrimal duct treated under direct observation.

This technique, termed dacryocystoscopy, is still experimental. However, further studies on patients are planned to assess its full potential.

Figure 12 Comparison of outer diameters (in mm, magnified 10×) of the fibrescopes and the commonly used Bowman's lacrimal probes. (Data have been kindly provided by KeyMed Ltd, Southend, UK and John Weiss and Son Ltd, Milton Keynes, UK.)



0·5 mm	1·1 mm	0·51 mm	0·69 mm	0·89 mm	0·98 mm	1·22 mm
PF-5	XTUF-11	00 00	00	1	2	3
Fibrescopes		Bowman's probes				

We are grateful to Mr Andrew Eakins of KeyMed Ltd, Southend, UK for providing the prototype fibrescopes and the recording equipment. We thank Mr J J Kanski, FRCS, for his critical reading of the manuscript.

The authors wish to declare that they have no commercial interest in any of the instruments/products used in this study.

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Copper levels in human mixed, nuclear brunescence, and posterior subcapsular cataract

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Abstract

The study was undertaken to determine the copper content in different human cataractous lenses. The level of copper increased with increasing age in nuclear brunescence and mixed cataractous lens and a low amount of copper was observed in the posterior subcapsular cataractous lens with increasing age. Cataractous lenses of females have greater amounts of copper compared with males.
(*Br J Ophthalmol* 1992; 76: 668–669)

Metals in human fluids and tissues are of potential importance not only in medical investigation but also in everyday clinical practice.[1] In recent times a role for trace elements in human nutrition has been identified and an involvement in different diseases.[2]

Most of the mineral elements previously regarded as physiologically inactive have now been found to participate in a variety of biological processes. Trace elements function primarily as catalysts in enzyme system in the cells. Of several trace elements, inorganic ions such as copper are essential virtually for all biochemical and physiological process in humans and they occur in minute amounts.[3]

The presence of trace elements such as copper in tissues was reported in the early part of century[4] and the role of copper in cataract formation has intrigued the biochemists and physicians for a long time.

Copper is essential for the activity of numerous enzymes such as cytochrome oxidase, superoxide dismutase, and uricase.[5] Derangements in copper metabolism and resulting changes in its concentration within tissues and body fluids have been associated with pharmalogical states.[6] The copper content of the human lens has been of particular interest because of its possible relation to cataractogenesis,[7] and it is found in elevated levels in the state of cataract maturity.[8]

The present investigation was undertaken to determine the levels of copper in posterior subcapsular nuclear brunescence of the mixed lens of males and females in different age groups.

Materials and methods

This investigation was carried out on 200 patients admitted to the various eye hospitals in Coimbatore during January to November 1991. The age and sex of patients were recorded and cataractous lenses were categorised as nuclear brunescence, posterior subcapsular (PSC), and mixed cataracts, as described by Oxford classification system.[9] The normal lenses were obtained from an eye bank located in Coimbatore and these were used as controls. The lenses were collected in glass containers, washed with Teepol, and rinsed with double distilled water to avoid contamination.

Each lens was oven dried and weighed separately. They were then digested in 3 ml of a digestion mixture of concentrated nitric acid and perchloric acid in the ratio 3:1. The mixture was then evaporated to dryness and to the precipitate was added 10 mmol nitric acid. The level of copper was estimated at 324·9 nm in an atomic absorption spectrophotometer.[10] All the mean values were analysed by *t* test to determine the significance.

Results and discussion

Increased levels of copper were observed in cataractous lenses compared with controls. The copper content was increased with increasing age but only in nuclear brunescence of the mixed cataractous lenses.

In females, cataractous lenses show higher levels of copper than males. The PSC cataractous lens (Table 1) showed a decrease in copper content at all ages with a mean value of 1·73 (SD 1·23) μg/g dry wt in males and a level of 1·93 (SD 1·35) μg/g dry wt in females in the age range 41–50 years. Gradually the copper content decreased as the age increased to 61–70 years with a mean value of 1·40 (SD 0·74) in males and 1·43 (SD 0·82) μg/g in females. All the mean values of PSC were higher than control values. It was seen in the case of nuclear brunescence cataract lenses (Table 2) that there was a higher copper content with increasing age with a maximum mean value of 2·11 (SD 1·68) μg/g in female lenses, and a maximum mean value of 2·00 (SD 1·50) μg/g in males. In mixed cataract lenses (Table 3) an increase in copper content with age was also observed. Here also, the mean value was higher when compared with the control group. These results showed that copper content is higher in

Table 1 Data showing the copper concentration in lenses with posterior subcapsular cataract in thre age groups (μg/g dry wt)

Sex	Parameter	No of lenses observed	Age group (years)	Copper concentration Mean	SD
Male	Control	50	41–50	1·32	0·70
		50	51–60	1·22	0·64
		50	61–70	1·20	0·52
	Experimental	100	41–50	1·73	1·23
		100	51–60	1·50	0·95
		100	61–70	1·40	0·74
Female	Control	50	41–50	1·40	0·73
		50	51–60	1·32	0·70
		50	61–70	1·23	0·58
	Experimental	100	41–50	1·93	1·35*
		100	51–60	1·54	1·05*
		100	61–70	1·43	0·82*

* Values significant at 5% level

Table 2 Data showing the copper concentration in lenses with nuclear brunescence cataract in three age groups (μg/g dry wt)

Sex	*Parameter*	*No of lenses observed*	*Age group (years)*	*Copper concentration Mean*	*SD*
Male	Control	50	41–50	1·30	0·62
		50	51–60	1·25	0·70
		50	61–70	1·18	0·23
	Experimental	100	41–50	1·90	1·23
		100	51–60	1·94	1·38
		100	61–70	2·00	1·50
Female	Control	50	41–50	1·34	0·73
		50	51–60	1·40	0·92
		50	61–70	1·26	0·64
	Experimental	100	41–50	1·95	1·45*
		100	51–60	2·05	1·54*
		100	61–70	2·11	1·68*

*Values significant at 5% level

Table 3 Data showing the copper concentration in lenses with mixed cataract in three age groups (μg/g dry wt)

Sex	*Parameter*	*No of lenses observed*	*Age group (years)*	*Copper concentration Mean*	*SD*
Male	Control	50	41–50	1·10	0·23
		50	51–60	1·22	0·64
		50	61–70	1·30	0·70
	Experimental	100	41–50	1·26	0·77
		100	51–60	1·45	1·12
		100	61–70	1·90	1·23
Female	Control	50	41–50	1·26	0·67
		50	51–60	1·45	1·12
		50	61–70	1·50	0·90
	Experimental	100	41–50	1·20	0·60*
		100	51–60	1·50	0·96*
		100	61–70	1·98	1·48*

*Values significant at 5% level

the nuclear brunescence cataractous lenses than the mixed cataractous lenses as age increases. The reverse is noted in PSC cataractous lenses where there is an increased amount of copper in the lower age group. Females have larger amounts of copper than males.

In the present study it was concluded that in mixed cataractous lenses the copper concentration increases with the increase in age. This confirms the study of Nath *et al.*[11] This increase was due to the inhibition of lactate dehydrogenase activity in the formation of cataract. The increase in copper content in senile lenses was also reported by Jain and Nath.[12,13] However, copper is important for various metalloenzymes such as cytochrome oxidase and aldolase, which are vital for the maintenance of cell growth.

A study of copper concentration of cataractous lenses in vertebrates reported no correlation between copper concentration and cataract.[7]

The nuclear portion of the lens has less copper[14] but this present study deviates from this statement. The increasing concentration of copper in the nuclear cataract lenses has also been reported elsewhere,[15,16] confirming the results of the present study. Shlopak[13] stated that the copper concentration in the cataractous lenses decreases as age increases; this is associated with more metabolic activity of lenses, but again this is not seen in the present study. Marraini and Mangoli[17] observed that in the cortical type of cataract the main features are the alteration of water content resulting in hydration of tissue.

The presence of excess levels of copper in cataract may oxidise sulphydryl groups to disulphides followed by a reduction of copper which may generate O_2^- radicals[15]; copper in higher concentrations can be toxic to cells.[18]

Copper ions, therefore, may be responsible for the damage to the lens capsule, thereby causing leakage of beta and gamma crystallins into the aqueous humour, and conversion to insoluble proteins during the process of cataractogenesis.[19]

In conclusion, the copper content increases with increasing age in nuclear brunescence and mixed cataractous lenses, and copper content and age are directly proportional to each other in these conditions. In the case of PSC cataract lenses the reverse is true.

Further investigation on the amount of trace elements present in cataract formation is needed.

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A new local anaesthesia technique for cataract extraction by one quadrant sub-Tenon's infiltration

J D Stevens

Abstract

A new technique of local anaesthetic administration has been used for 50 patients undergoing cataract extraction. The simple technique involves direct transconjunctival infiltration of local anaesthetic directly to the sub-Tenon's space, in the inferior-nasal quadrant, using a blunt 19-gauge Southampton cannula. This method seeks to avoid the risks of retrobulbar haemorrhage, perforation of the globe, damage to the optic nerve, and injection into the subarachnoid space, whilst providing prolonged and reliable anaesthesia. Akinesia is achieved by the inferior-nasal placement of solution and if not sufficient, a top-up can easily be given. Patients graded any discomfort or pain using a 10 cm visual analogue graphical pain score chart with numerical and descriptive rating scale. The delivery of 50:50 mixture of lignocaine 2% and bupivacaine 0·5% anaesthetic was evaluated by patients with a median response of 'slight discomfort'. The operative procedure was graded with a median of 'no pain or discomfort', both for extracapsular cataract extraction and phakoemulsification. This is a new, modified, sub-Tenon technique which is simple, reliable, and which offers excellent anaesthesia and akinesia and avoids a sharp instrument being passed into the orbit.

(*Br J Ophthalmol* 1992; **76**: 670–674)

In 1884 Knapp reported successful cataract extraction by topical anaesthesia using frequent drops of 5% cocaine. He commented on the need for more extensive anaesthesia if the iris is to be anaesthetised. Describing a technique for enucleation, he reported the successful use of a retrobulbar injection,[1] rotating the globe nasally and introducing a needle through the muscle cone temporally. In 1884 Turnbull also described a local anaesthetic technique for enucleation, where topical 4% cocaine was applied to the cornea and conjunctiva, followed by the opening of Tenon's fascia and cocaine being dropped into the cut.[2] Blunt pointed scissors which were curved on the flat were introduced from the nasal side and drops instilled. This was reported as successful in causing anaesthesia and vasoconstriction.

Today various methods of local anaesthesia are in use for cataract extraction including retrobulbar,[3] peribulbar,[4] subconjunctival,[5] and sub-Tenon's[6] application of local anaesthetic solution. The desire to find an alternative to retrobulbar anaesthesia has been caused by a variety of unusual but potentially severe complications arising with this technique,[7 8] including globe perforation, retrobulbar haemorrhage, and accidental injection of solution into a blood vessel or the subarachnoid space.

Peribulbar anaesthesia has been advocated to reduce risk of respiratory arrest and other systemic complications associated with retrobulbar anaesthesia and since the muscle cone is not entered, local anaesthetic solution is delivered away from the globe, so minimising risk to the eye. Anaesthesia is achieved by diffusion, often requiring a greater volume of solution than for true intraconal retrobulbar anaesthesia. In spite of an injection positioned away from the globe, peribulbar anaesthesia has been reported to be associated with serious complications, including globe perforation.[9 10]

For both retrobulbar and peribulbar techniques a sharp, or relatively sharp, needle is 'blindly' placed into the orbit to deliver the anaesthetic solution. To avoid injecting deep into the orbit subconjunctival anaesthesia has been advocated, involving a subconjunctival injection of anaesthetic at the 12 o'clock position[5 11 12]; this technique also being termed limbal subconjunctival injection.[13] In a co-operative patient able to maintain ocular position, topical and subconjunctival anaesthesia have been shown to be effective in providing anaesthesia though more conjunctival chemosis occurs with subconjunctival than with retrobulbar or peribulbar anaesthesia.[14] Many ophthalmic surgeons are reluctant to adopt a technique that does not provide sufficient ocular akinesia and in patients less able to understand the requirements of the ophthalmologist, or who are anxious and unable to communicate properly, general anaesthesia or a technique involving good akinesia is desirable. Residual ocular muscle function not only allows unexpected globe movement during surgery but may increase intraocular pressure.

Direct sub-Tenon's delivery of solution using a blunt cannula offers an alternative method. For retinal surgery[15] and for cataract extraction[6] a technique has been described where the conjunctiva is anaesthetised by subconjunctival injection of local anaesthetic solution and then Tenon's fascia is opened using blunt Westcott scissors. A blunt 19 gauge cannula directly irrigates solution posterior to the globe. In the case of retinal surgery, solution is delivered to all four quadrants[5] and for cataract surgery[6] the superior quadrants have been used.

A simple technique that produces excellent anaesthesia and reliable akinesia, with minimal risk of perforation of the globe, is the ideal. This paper describes a single quadrant inferior-nasal sub-Tenon's approach with a blunt cannula which is a modification of the original idea of Turnbull,[2] the four quadrant method of Mein and Woodcock,[15] and the superior quadrant method of Hansen *et al.*[6] It has been developed to

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be an effective and minimal risk anaesthetic technique for cataract surgery.

Method

Fifty patients who underwent cataract extraction with posterior chamber lens implantation who were scheduled for local anaesthesia, had an anaesthetic blockade by direct blunt cannula sub-Tenon's delivery. After informed consent, in the holding bay within the operating theatre suite, four drops of topical amethocaine 1% were applied to the cornea and conjunctiva followed by one drop of adrenaline 0·1%. A blunt Westcott (spring) scissors was taken and a small 'nick' incision made in the conjunctiva in the inferior-nasal quadrant approximately 5 mm from the limbus (Fig 1). A blunt 19 gauge Southampton curved cannula was used to deliver a small bleb of local anaesthesia, using a 50:50 mixture of lignocaine 2% and bupivacaine 0·5% without adrenaline. This facilitates identification and elevation of Tenon's fascia and fine underlying intermuscular septal fascia. The Wescott scissors are then slid through the nick in the conjunctiva and used to create another 'nick' taking care to create a path in Tenon's capsule and the intermuscular septal fascia. Moorfields forceps are used to grip the conjunctival edge where the small nick was made and the curved cannula is then inserted onto bare sclera and glided along a path following the contour of the globe, until posterior to the equator (Fig 2). It is very important to pass through conjunctiva, Tenon's fascia, and the intermuscular septum, to reach bare sclera and therefore into the Tenon's space, before sliding the cannula posteriorly. Often, after the cannula is passed back in the potential space between the intermuscular septum, Tenon's, and sclera, a resistance is felt owing to fascia adherent to sclera posterior to the equator. This tissue may be passed through by application of gentle pressure to the syringe and after a few seconds a slight 'give' is felt, solution begins to flow, and the cannula may be further advanced. After delivery of approximately 1 ml, at this level, just posterior to the equator, the cannula is advanced further to a total distance of approximately 1·5 to 2·0 cm, depending upon globe size, and further solution delivered to a total volume of 3·0 to 3·5 ml. At this stage a small degree of proptosis of the globe is usually visible, this providing confirmation that the solution has been delivered to the correct place. If care is not taken to deliver solution to the posterior sub-Tenon potential space, then it is very easy to deliver anaesthetic solution as an anterior subconjunctival application. Immediate conjunctival chemosis then results and this may be extensive if the whole volume is given anteriorly by mistake. It is important therefore for the volume to be given slowly and in graded steps, so ensuring that the site of delivery is that which was intended. With practice, the cannular position, with respect to the fascial layers, can be judged accurately by the operator and the technique becomes quicker and easier.

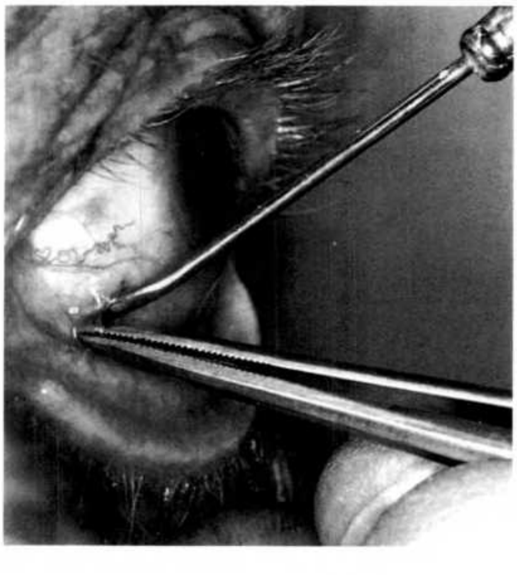

Figure 1 A blunt Westcott (spring) scissors is taken and a small 'nick' incision made in the conjunctiva in the inferonasal quadrant approximately 5 mm from the limbus. A blunt 19 gauge Southampton curved cannula is used to deliver a small bleb of local anaesthesia, so raising Tenon's capsule allowing better visualisation.

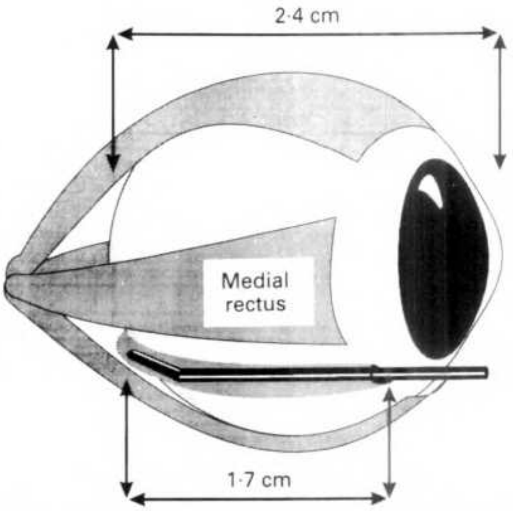

Figure 2 Schematic diagram of the path of the Southampton cannula, following the contour of the globe, to deliver anaesthetic solution posterior to the equator.

After giving the anaesthetic solution at least 15 minutes was allowed for diffusion to occur before commencing surgery. Immediately prior to surgery, assessment of the amount of akinesia, presence and degree of ptosis, and eyelid tone was made. Akinesia was assessed by a non-masked, four category, subjective scale graded as complete movement remaining, moderate movement, slight movement, no movement. If the eyelids were not flaccid immediately prior to surgery, an additional Van Lint facial block was given.

Each patient was shown a 10 cm visual analogue graphic pain score chart, on the first postoperative day, with numerical and descriptive rating scale, graded from 0 to 10 (Fig 3). Patients were shown the chart and invited to score where on the chart they could grade any discomfort or pain experienced. If patients were unable to see the chart, or read the accompanying text (printed at N10 size), a verbal explanation and description of the scoring chart was performed. Patients were first requested to score verbally any pain or discomfort for the delivery of the anaesthetic and then separately score the operation itself.

Anatomy

Connecting the extraocular muscle capsules is a sheet of condensed fascial tissue, the inter-

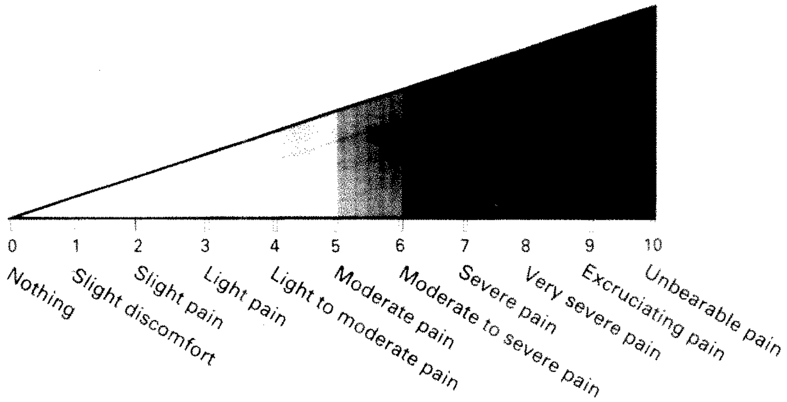

Figure 3 Visual analogue graphic pain score chart. A 10 cm pain score chart with numerical and descriptive rating scale.

muscular septum. As the extraocular muscles pass forward they increase in separation from each other, but the intermuscular septum continues to connect them. External to the extraocular muscles is a fascial plane, the Tenon's capsule.[16] Tenon's capsule is a relatively dense fascial layer of elastic connective tissue surrounding the globe and extraocular muscles extending from the limbus to the optic nerve. All the extraocular muscles penetrate Tenon's capsule, the four recti penetrating posterior to the equator. Tenon's capsule anterior to this has been termed the anterior portion and extends to the limbus. A posterior portion of Tenon's capsule extends from the rectus penetrations back to the optic nerve and is thinner. The inner surface of the posterior portion of Tenon's capsule apposes sclera as there is no sub-Tenon's intermuscular septum present. A potential space exists between sclera and Tenon's capsule, the Tenon's or episcleral space, which does not normally contain any fluid. The anterior Tenon's capsule and sclera are separated by the intermuscular septum which extends between the extraocular muscle capsules in the same way as between the muscles in the posterior orbit. At about 3 mm from the limbus the anterior Tenon's capsule and sub-Tenon's intermuscular septum fuse to form a single fascial plane which further fuses with conjunctiva 1 mm from the limbus. Incision further back than 3 mm from the limbus must pass through all three layers. Incising conjunctiva closer than 3 mm from the limbus allows one incision to pass through conjunctiva, Tenon's capsule, and the intermuscular septum simultaneously. This would be an advantage to easily reach bare sclera, but by cutting the conjunctiva further back at approximately 5 mm from the limbus, less of a curve is required for the path of the cannula as it follows the contour of the globe. There is less trauma to the conjunctiva with a direct posterior path, with less risk of conjunctival tearing.

Tenon's space delivery allows potential diffusion of the solution throughout this compartment, and solution may also diffuse back into the orbit, reaching the intraconal central region. Koorneef has stated that there is no clear cut compartmentalisation into central (retrobulbar) region and peripheral space outside the muscle cone, not finding a common muscle sheath by serial section study.[17] Solution may then diffuse extensively between compartments if sufficient time is allowed and may be facilitated by use of hyaluronidase.[15] Hyaluronidase has not been used in this study owing to difficulties in supply during the period of the study, though when available it would be anticipated that its use may enhance the efficacy of the technique.

To eliminate pain sensation for the globe, pain fibres exiting from the eye must be blocked and to further achieve akinesia, the extraocular muscle nerve supply should also be inhibited. Ocular pain sensation is mediated by the long sensory root of the ciliary ganglion. These fibres pass through the ganglion and provide sensation from the cornea, iris, and ciliary body.[18] The ciliary ganglion is situated posteriorly in the orbit approximately 1 cm anterior to the optic foramen between the optic nerve and the lateral rectus muscle within the muscle cone. It is separated from the lateral rectus muscle by loose fat and is close to the ophthalmic artery. Posterior diffusion of local anaesthetic solution may directly block the ganglion, or blockade of muscle function may occur by solution affecting nerves passing more anteriorly. The differential temporal decrease in muscle function, with those muscles closest to the site of solution delivery, medial and inferior rectus being lost first, suggests that a direct block upon anterior nerve fibres may be occurring.

The extraocular muscles are supplied by cranial nerves III, IV, and VI. To achieve akinesia, motor fibres within these nerves have to be inhibited at some level in their path. Superior rectus is supplied by the superior division of the oculomotor nerve entering the inner surface of the muscle at the junction of its middle and posterior thirds.[19] Inferior rectus, medial rectus, and inferior oblique are supplied by the inferior division of the oculomotor nerve entering the inner surface of the muscles at the junction of the middle and posterior thirds. Lateral rectus is supplied on its inner aspect by the abducens nerve just behind its middle. Only superior oblique is supplied superiorly at its lateral border by the trochlear nerve, the most anterior branch being at the junction of the posterior and middle thirds. All extraocular muscles, except superior oblique, are thus supplied by nerves entering on the inner surface. The presence of superior oblique function after effective blockade of all other extraocular muscle activity provides further evidence that a direct action upon nerve fibres in the retrobulbar compartment is the mechanism of action. To what degree the anaesthetic solution affects the ciliary ganglion is undetermined.

Results

Fifty consecutive patients who received local anaesthesia for cataract extraction had sub-Tenon's anaesthesia and none experienced a problem of excessive discomfort on delivery of the block. Thirty four patients underwent extracapsular cataract extraction and 16 phakoemulsification, all with posterior chamber lens implantation. All local anaesthetic blocks were performed by the author and no complication occurred which prevented surgery. No failures in anaesthesia occurred which would have necessitated supplemental anaesthesia using

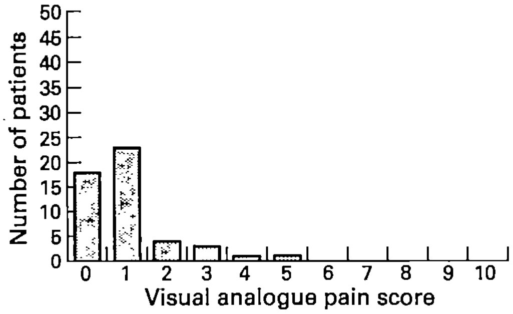

Figure 4 Pain scores recorded for the delivery of the sub-Tenon local anaesthetic block. Eighteen patients recorded no pain or discomfort and a further 23 only slight discomfort.

peribulbar infiltration. No patients who were scheduled for local anaesthesia were considered unsuitable for the one quadrant sub-Tenon's anaesthetic technique.

Pain scores assessed using the visual analogue score chart produced a median score of 1 ('slight discomfort') and mean of 1·0 for the delivery of the sub-Tenon's block (Fig 4). Eighteen patients graded no pain or discomfort and 23 only slight discomfort, with no patient grading greater than 5. Patients subjectively described the giving of the block most often as a feeling of 'slight pressure'.

For the subsequent operative procedure the median pain score was 0 ('no pain or discomfort') and the mean 0·3 (Fig 5); 41 patients scored 0 indicating the effectiveness of local anaesthesia felt during the operation. The one patient who gave a score of 7 ('severe pain') described the operation as pain free and would have scored it as 0 but felt sudden pain at the end of the operative procedure on giving subconjunctival injections. There was no difference of median pain scores between those having extracapsular extraction and phakoemulsification (median score of 0).

The anaesthetic block had no visible effect on superior oblique muscle function which remained for all 50 patients, though 27 patients developed otherwise complete akinesia. Those patients with incomplete akinesia most often had preserved lateral rectus muscle function. In patients where akinesia was not deemed sufficient by the surgeon (eight patients), a further 1–1·5 ml of solution was delivered to the original sub-Tenon site. Excellent anaesthesia and good akinesia was then achieved within 5 minutes of delivery of the top-up and the operative procedure then commenced.

More conjunctival chemosis subjectively occurred than usually seen with peribulbar or retrobulbar anaesthesia and subconjunctival haemorrhage extending to more than one quadrant, assessed at the commencement of surgery, occurred in 16 patients (32%). The use of adrenaline 0·1% immediately prior to the conjunctival incision is performed to attempt to reduce any subconjunctival haemorrhage by blanching conjunctival vessels. Complete ptosis occurred in 18 patients and partial ptosis in 15. Twenty three patients had an additional Van Lint facial block, subjectively based upon the presence of remaining eyelid tone after the sub-Tenon block, immediately prior to surgery.

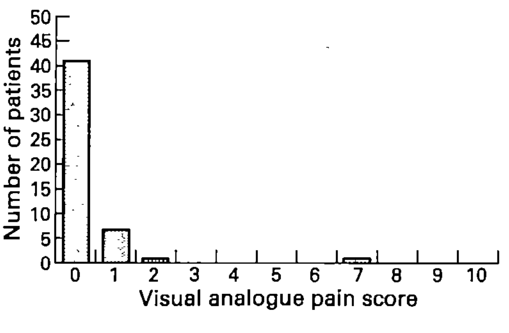

Figure 5 Pain scores recorded for the operative procedure. Forty one patients recorded no pain or discomfort, only one patient describing significant pain with a score of 7.

Discussion

The delivery of sub-Tenon's anaesthetic, directly irrigating the immediate retrobulbar region, is effective and reliable in providing both for anaesthesia and akinesia. Patients find not having an injection through skin, simple and relatively painless, except for those receiving a further facial block.

The method for sub-Tenon's irrigation described in this paper differs from that of Hanson *et al*,[6] in that anaesthetic is delivered to the inferior-nasal quadrant and no further opening of conjunctiva is performed. Hanson *et al* raise a conjunctival bleb by subconjunctival injection using a sharp needle, before incising superior conjunctiva, and then delivering sub-Tenon solution. If limbal or scleral based cataract section is employed, superior quadrant application provides a simple method of delivery of solution peroperatively, though excess application of solution may result in a 'bulgy' eye if applied immediately prior to commencing intraocular surgery.

If solution is delivered to either of the superior quadrants possible chemosis and subconjunctival haemorrhage may affect visualisation of the operative section. Therefore it would be desirable to deliver anaesthetic to an inferior quadrant. The inferior temporal vortex vein emanates from the sclera 8 mm posterior to the inferior rectus muscle insertion at its temporal border. It then loops on the inner surface of Tenon's capsule and it may be damaged if entry into this quadrant is made without knowledge of the presence of the vein. The inferior-temporal quadrant is complicated by the presence of the inferior oblique muscle which passes up to run under lateral rectus. The inferior nasal quadrant also has a vortex vein but this is posteriorly situated and does not loop in the same way as the inferior temporal vortex vein. Entering conjunctiva inferiorly also avoids damage to superior conjunctiva, which is an important consideration if future glaucoma filtering surgery is to be performed, or a filtering bleb is already present. The inferior nasal quadrant has thus been chosen as the best quadrant to site delivery of anaesthesia, being the least likely to cause complication.

After delivery of the local anaesthetic solution surgery was performed no earlier than 15 minutes later, though anaesthesia has been described as occurring after only a few minutes using a different sub-Tenon's technique for panretinal photocoagulation.[20] The 15 minute delay between delivery of block and commencement of surgery was to allow the solution time to diffuse, to achieve anaesthesia, akinesia, and to reduce any excess intraconal pressure on the globe. On application of the one quadrant block some proptosis is usually seen and the space occupying effect of the 3 ml delivered would be expected to give some *vis a tergo* vitreous pressure which may give rise to a 'bulgy eye' if surgery were to begin immediately.

Possible problems associated with this inferior-nasal technique of anaesthesia include the requirement for the patient to elevate or abduct the eye to expose the inferior-nasal quadrant and allow the cannula to pass backward, though no patients during this study had any difficulty with this manoeuvre. Some peroperative chemosis is inherent with this technique and may be limited by ensuring posterior delivery of anaesthetic solution. Careful posterior delivery of anaesthetic not only prevents any chemosis extending to the region of the cataract section but also ensures that the block is truly delivered to the posterior sub-Tenon's space and not inadvertently to the anterior subconjunctival space. An incision into conjunctiva and underlying fascia is made and a theoretical risk of providing a route for infection is possible, though any ocular surgery would normally have antibiotic cover by topical treatment which would also provide cover for this small incision.

Subconjunctival haemorrhage is caused by fine vessels which are inevitably severed on making the conjunctival cut. Though a visible haemorrhage may occur, it was often small and extended over one quadrant, though the opening of a subconjunctival route for haemorrhage to spread is facilitated by anteriorly leaking anaesthetic solution separating tissue planes. Though the haemorrhage was able to spread, it was in a thin layer and no patients had sufficient subconjunctival haemorrhage to cause a problem. Patients using anticoagulant medication, however, would require careful assessment before using the sub-Tenon technique due to the potential for haemorrhage from a severed conjunctival vessel. Use of the blunt cannula irrigation technique should, however, provide more safety, if local anaesthesia is used, than a sharp needle local anaesthesia technique.

One patient in this study had prior ocular surgery for retinal detachment. No difficulty was encountered with the delivery of the block except some Tenon's dissection was required to achieve a satisfactory sub-Tenon avenue for solution delivery. From the results of sub-Tenon's anaesthesia in vitreoretinal surgery, the presence of scleral buckles, or previous surgery resulting in adhesions of Tenon's fascia, does not appear to present a problem with this form of block other than that extra dissection may be required.

Using a 50:50 mixture of lignocaine 2% and bupivacaine 0·5% the blocks have been found to have a rapid onset within a few minutes and to last a considerable length of time with some patients taking many hours to recover full ocular movements. The mean operative time for phakoemulsification was longer than for extracapsular extraction but the blocks remained effective for the duration of both procedures. In view of the efficacy of the block and the presence of ptosis, no additional facial block was used in 27 patients. To prevent risk of postoperative corneal exposure a dressing using a pad and covering shield were used routinely at the end of the procedure.

Anterior diffusion of solution to the subconjunctival space occurs by anterior solution delivery on forming the initial bleb and forward seepage of solution through the sub-Tenon path created by the infusion cannula. This gives rise to the observed subconjunctival chemosis. The conjunctival incision site provides a convenient, well-anaesthetised site to place a subconjunctival injection at the end of the operative procedure.

With familiarity the technique is relatively simple and quick to perform, offering excellent anaesthesia and akinesia, avoiding a sharp instrument being passed into the orbit. It provides a technique where the risk of accidental injection of solution to the subarachnoid space, into a blood vessel or of globe perforation should be practically eliminated, owing to use of the blunt cannula.

After over 100 years of sharp instrument local anaesthesia, a direct sub-Tenon irrigation approach, such as described here, could be viewed as returning full-circle to a modification of one of the first local anaesthetic techniques ever employed for ophthalmic surgery.[2]

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One stage adjustable sutures: practical aspects

S T Ruben, J S Elston

Abstract

Strabismus surgery using one stage adjustable sutures was carried out under local anaesthesia in six patients with good results. The criteria for patient selection and the surgical technique are discussed.

(*Br J Ophthalmol* 1992; 76: 675–677)

Since their re-introduction by Jampolsky in 1974,[1] adjustable suture techniques have been widely used and the indications, stability, and benefits of the technique well documented.[2-5]

In general, a two stage procedure is used in which the estimated amount of muscle recession or resection is performed at the time of surgery and then adjusted some time later, usually between 5 and 24 hours postoperatively. Though the one stage procedure using only topical anaesthesia is not new,[6] attitudes towards the use of a single stage operation with adjustment taking place at the time of surgery have turned full circle and with the present desire to keep hospitalisation to a minimum and remove the risks associated with general anaesthesia the one stage procedure has more recently been resurrected.[7] Though the outcome and stability of this technique matches that of the two stage operation,[8] the practical aspects associated with the single stage operation are not well documented.

We describe our experience in six consecutive cases successfully operated on using the technique and discuss the indications and method.

Patients, materials and method

Six consecutive patients with non-concomitant strabismus underwent surgery under local anaesthesia after full informed consent. The decision to use local anaesthesia was made either on medical grounds or at the request of the patient. Of the six patients, three had squints secondary to peripheral pathology; dysthyroid eye disease (two cases), and cataract surgery, while three had central causes; internuclear ophthalmoplegia, pontine exotropia, and skew deviation. The number of muscles operated on ranged from one to four.

No predmedication was used in any of the cases. A cardiac monitor was used in every case, but there were no problems encountered from the effects of the oculocardiac reflex. Local anaesthesia consisted of topical amethocaine 1% applied every 5 minutes for six applications prior to surgery and then continued at frequent intervals throughout the procedure. This was supplemented by subconjunctival infiltration of 0·1–0·2 ml 2% lignocaine with adrenaline 1:200 000 over the insertions of the muscles to be operated on.

The skin was cleaned with povidone iodine solution and fenestrated surgical drapes applied to allow adequate exposure. A plastic steridrape was used to keep the eyelashes away from the operative field. A lid speculum was inserted. Stay sutures of 5/0 silk were put through the episclera at the limbus to allow manipulation of the eye. The conjunctiva was opened over the muscle insertion and the muscle isolated taking care not to pull directly on it. The muscle was secured using double-ended 6/0 vicryl suture on a spatulated needle and knotted at each side. After the muscle had been divided from its insertion, and haemostasis secured using bipolar diathermy, the sutures were passed back through the insertion once only. The amount of recession/resection was estimated and the suture tied with a double throw and half bow knot. At this stage the lid speculum was removed and adjustments made as necessary. The position of the eyes was tested using the cover test for near and distance with the patient in the supine position using a suitable fixation target on the ceiling, together with the patient's subjective reports of single vision. The cover test was performed by the assistant so that the surgeon did not need to rescrub after each cover test. Where vertical muscles were involved the cover test was also performed in downgaze. Horizontal deviations were adjusted as far as possible towards orthophoria, whilst vertical deviations involving the inferior rectus were left slightly undercorrected so that the eyes were straight in primary and downgaze positions. This was to

Table 1 *Results of the six cases*

No	*Age*	*Sex*	*Cause of squint*	*Pre-op orthoptics*	*Surgery*	*Post-op orthoptics*	*Comments*
1	83	F	Post ECCE L+R	L/R 16–20 PD	R. IR −4	Straight	Diplopia relieved
2	74	F	Dysthyroid	L/R 12–15 PD	R. IR −3	Straight	Diplopia relieved
3	80	F	Dysthyroid	ESO 14–30 PD R/L 12–20 PD	L. MR −max L. IR −3	ESO 8–16 PD	Improved area of BSV
4	35	M	Bilateral INO skew deviation	EXO 4 PD R/L 12 PD	L. IR −4	6 M straight 1/3 M min L/R	Symptomatically improved INO persists
5	55	M	L. INO	EXO 23–35 PD	L. MR +4 L. LR −3	Straight in 1° position	INO persists
6	76	M	Pontine exotropia	EXO 55–65 PD	R+L MR +5 R+L LR −5	Straight	Patient symptom free

ECCE=extracapsular cataract extraction; PD=prism dioptres; IR, MR, LR=inferior, medial, lateral rectus; INO=internuclear ophthalmoplegia.

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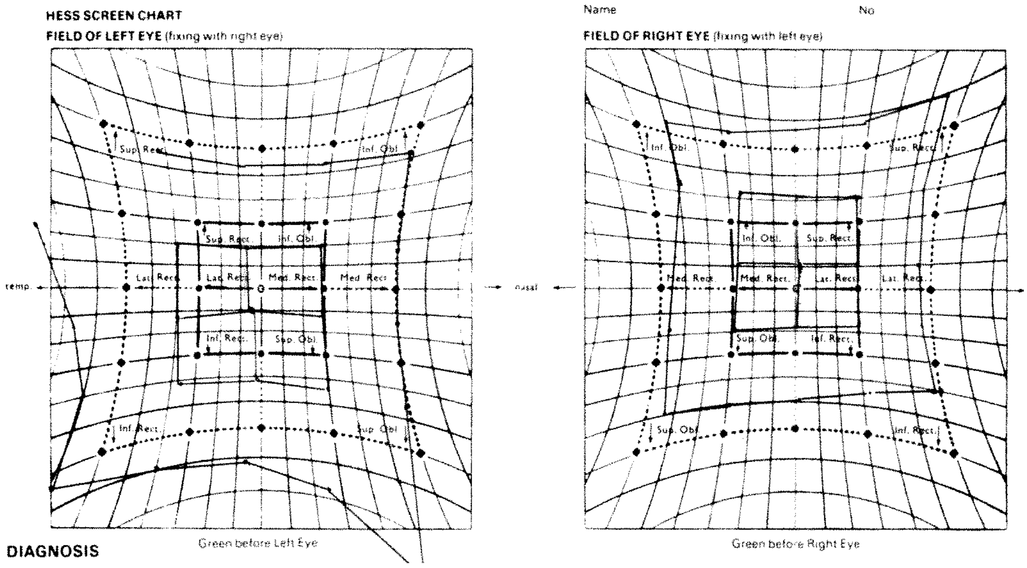

Figure 1 Preoperative Hess chart.

allow for the late overcorrection that can occur with inferior rectus recessions.[9]

Results

The results of the six cases are presented in Table 1. Follow up ranged from 3 months to 1 year. At 3 months the results had stabilised in all patients and none required further surgery.

All patients experienced discomfort of varying degrees but all were able to tolerate the procedure with little complaint. The most discomfort was associated with stretching of the rectus muscles. One patient experienced considerable postoperative pain requiring strong analgesia.

In one patient the infiltration of local anaesthetic caused subconjunctival haemorrhage which made muscle isolation more difficult and prolonged the procedure. It was also noted that at the time of adjustment the pupil of the operated eye had become significantly dilated as a result of the adrenaline.

Adjustment was difficult if attempted immediately after the operating lights had been turned off owing to bleaching of the macular pigments, and this was especially so in one patient with a degree of age-related macular degeneration. The adjustment stage was made easier if the operating lights were angled from the side, rather than directly above, during the earlier stages of the operation.

CASE REPORT

A 35-year-old driving instructor presented with skew deviation and bilateral internuclear ophthalmoplegia following tuberculous meningitis. He had visual acuities of 6/6 in both eyes and a right divergent squint with right hypertropia. Prism cover test showed the horizontal deviation to measure 10 prism dioptres (PD) for near, 25 PD distance, while the vertical deviation measured 12 PD. His complaint was of vertical diplopia and with a 12 PD Fresnel prism base down in front of the right eye he was able to obtain binocular single vision. A month later the horizontal deviation had corrected leaving the vertical deviation stable at 12 PD. He was admitted for surgery 6 months later as the deviation remained stable (Hess chart, Fig 1). The left inferior rectus was recessed approximately 4 mm and adjusted to orthophoria in the primary and downgaze positions. Four months after surgery the deviation is stable and the eyes

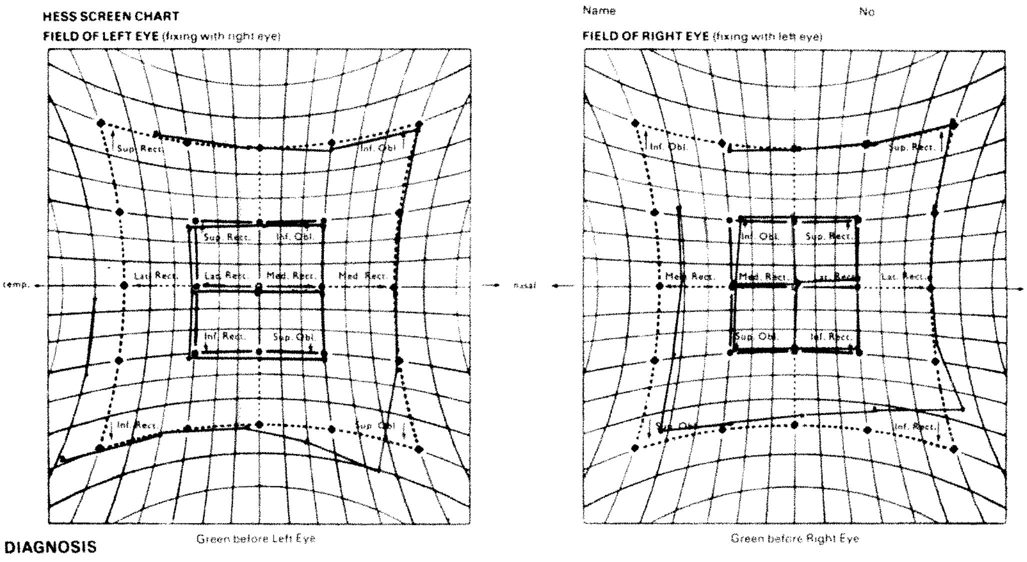

Figure 2 Postoperative Hess chart.

straight on cover test. However some torsional element remains and requires the use of 3 PD prism for reading. The improvement is shown in the postoperative Hess chart (Fig 2).

Discussion

The principal indications for adjustable sutures are well documented and include most types of complicated strabismus. In this series the type of cases selected fell into two groups. Those with a localised cause, either dysthyroid eye disease or following cataract surgery, and those in which the strabismus was secondary to a central disorder of eye movement – internuclear ophthalmoplegia, skew deviation, or pontine exotropia. The results show that surgery is an effective way of treating this second group of patients providing they have a stable deviation.

The one stage procedure is particularly appropriate when general anaesthesia is contraindicated or when a patient expresses a preference for local anaesthesia. However there are limitations. The number of muscles that can be operated upon should probably be restricted to two in each eye as the patient will find surgery lasting longer than 1 hour difficult to tolerate. Eyes that have had previous surgery need special consideration as scarring may entail a difficult dissection which is likely to be time consuming and more painful.

The one stage procedure described is well tolerated by patients despite the lack of premedication. Mild hypnotics such as temazepam may have unpredictable effects and cause drowsiness which would interfere with the adjustment process. β blockers may relieve the peripheral manifestations of anxiety, but patients may have been selected for local anaesthesia because of general medical conditions in which their use is contraindicated. The possibility that β blockers could exacerbate the oculocardiac reflex should also be considered. The local anaesthetic described is effective on the conjunctiva and other tissues including the muscles but pulling on the muscles during resection remains unpleasant.

Postoperative pain was severe in two cases (one with four muscles operated on, one with two). This should be taken into account and adequate analgesia be made available in the postoperative period, especially if the procedure has been performed on a day surgery basis.

There are a number of problems particularly associated with one stage adjustment. There are visual factors resulting from reduced vision in the operated eye. These include a reduction in corneal clarity from corneal drying, abrasions or blood, pupillary dilatation due to adrenaline used in conjunction with the local anaesthetic, and bleaching of the macular visual pigments by the operating lights. This can be overcome by directing the lights from the side during the operation, and turning them off during the adjustment process. The distance fixation target cannot be set at 6 metres if the adjustment is done in the supine position, but this does not seem adversely to affect the outcome. The procedure is not suited for a single surgeon since a second person is needed at the adjustment stage, either a second surgeon or orthoptist. There is a possibility that the anaesthetic could alter muscle actions, though our results do not show any significant effect. This is more likely with the addition of subconjunctival anaesthesia. Finally, it is important to maintain the anaesthetic throughout the adjustment procedure.

The one stage procedure is technically difficult for the surgeon for these reasons. It is also demanding for the patient both in terms of pain and apprehension when two or more muscles are operated on, and in the difficulty of assisting the surgeon to achieve the correct suture tension owing to reduced vision in the operated eye. In conclusion, this method is suitable only for selective cases but is probably the treatment of choice for a single vertically acting muscle recession.

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British Journal of Ophthalmology 1992; **76**: 678–680

A photometric study of the effect of pupil dilatation on Nd:YAG laser iridotomy area

B W Fleck, E Fairley, E Wright

Abstract

A photometric study of the effect of pupil dilatation on Nd:YAG laser iridotomy area was performed in 21 eyes of 21 patients. The iridotomy area was 0·075 (0·055) mm^{-2} (mean (SD)) before pupil dilatation and 0·073 (0·070) mm^{-2} after pupil dilatation (*t* test NS). Iridotomy area after pupil dilatation correlated with iridotomy area before pupil dilatation (r=0·815, p<0·01) but did not significantly correlate with measures of iridotomy shape or position, or with changed iris area following pupil dilatation. Two iridotomies became reduced to less than 20% of their initial area following pupil dilatation. Our findings suggest that the only effective method of avoiding development of unacceptably small iridotomy area after pupil dilatation is to create a sufficiently large iridotomy at the time of initial laser surgery.

(*Br J Ophthalmol* 1992; **76**: 678–680)

Acute angle closure glaucoma may develop in the presence of a small but patent argon[1,2] or Nd:YAG[3,4] laser iridotomy. While acute angle closure glaucoma following operative peripheral iridectomy has generally been attributed to plateau iris syndrome,[5-7] not all cases of acute angle closure glaucoma following a small laser iridotomy can be placed in this category.[1,3,4,8]

The mechanism of failure of very small iridotomies may be related to obstruction of aqueous flow at very small iridotomy size.[9] Below a critical surface area significant iris bombé may occur at normal aqueous flow rates. When iris bombé is sufficient to cause iridocorneal contact throughout a critical extent of the angle, acute angle closure glaucoma results.[10,11] The minimum 'safe' size of iridotomy has not been defined, but an approximate value may be calculated using a simple mathematical model.[9]

One factor which might contribute to the area of an iridotomy falling below a critical level is the change in iridotomy configuration which occurs on pupil dilatation. We have performed a photometric study of the effect of pupil dilatation on iridotomy area in 21 eyes of 21 patients.

Materials and methods

Eyes studied had been treated by Nd:YAG laser iridotomy for chronic angle closure glaucoma or were fellow eyes. Eyes with a previous episode of acute angle closure glaucoma were excluded. A Zeiss 'Visulas' Nd:YAG laser and Zeiss anterior segment YAG contact lens were used to perform all iridotomies. The treatment site was in the superior iris, between 10 and 2 o'clock, approximately two thirds distance from the pupil margin to the base of the iris. A single 5–10 mJ pulse was delivered to the treatment site. If this pulse did not penetrate the iris, further single pulses were delivered to the same site until penetration was achieved.

A photometric technique was devised to analyse changes in iridotomy area following pupil dilatation. Only one eye from each patient was studied. When both eyes were suitable for study only the right eye was used. Informed patient consent was obtained prior to enrolment. The horizontal corneal diameter was measured using a Haig Streit slit-lamp measuring eyepiece, which incorporates a graticule with 0·1 mm divisions. The cornea and iris were then photographed using a Zeiss anterior segment camera. Photographs were taken at both the 0·65 and 1·8 magnification settings.

The pupil was dilated using one drop of tropicamide 1% and the eye was again photographed, using identical camera settings.

Colour transparency photographs were prepared, and projected onto a white screen. The projected horizontal corneal diameter of 0·65 magnification photographs was measured in millimetres, and compared with the measurement obtained using the slit-lamp measuring eyepiece. A magnification factor for the projected image was derived from these measurements for each patient. The magnification factor was approximately ×80 in every case.

The following measurements were made using a millimetre scale set on the projected image, and converted to unmagnified values using the magnification factor:

– horizontal pupil diameter, pupil undilated

– horizontal pupil diameter, pupil dilated

– distance from limbus to nearest point of iridotomy, pupil undilated

– distance from limbus to nearest point of iridotomy, pupil dilated.

Photographs at ×1·8 magnification setting were used to study the iridotomy site. The magnification factor used for these measurements was greater by a factor of ×2·77 (1·8/0·65). A millimetre scale was used to measure:

– iridotomy diameter in the longest and shortest axis, pupil undilated

– iridotomy diameter in the longest and shortest axis, pupil dilated.

The area of full thickness iridotomy before and after pupil dilatation was measured by placing millimetre graph paper on the white screen and counting the number of squares covered by the image of the iridotomy.

Linear regression analysis was used to detect significant correlations between changes in iridotomy area on dilating the pupil and a variety of parameters which might potentially influence this.

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Figure 1 (A) Reduction of iridotomy area following pupil dilatation. Pupil undilated. Area of full thickness iris patency indicated by arrow. Iridotomy area 0·027 mm^{-2} (B) Reduction of iridotomy area following pupil dilatation. Pupil dilated. Area of full thickness iris patency indicated by arrow. Iridotomy area 0·003 mm^{-2}.

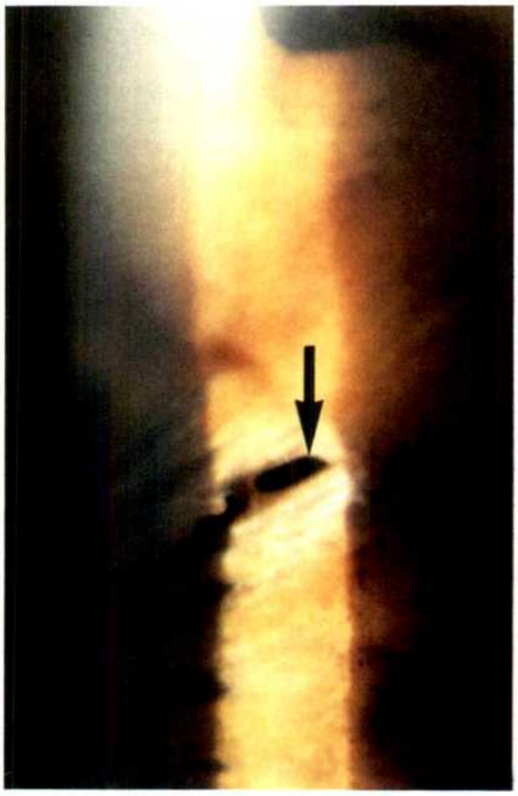

Fig 1A

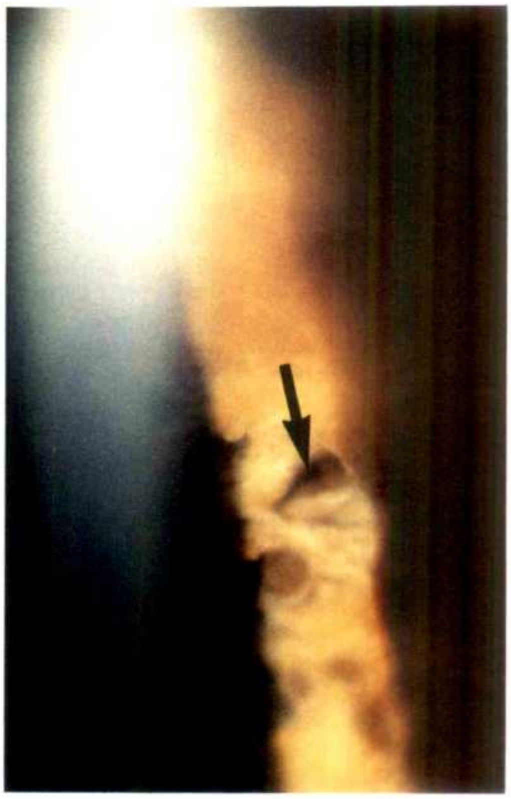

Fig 1B

Results

Photographs of 21 eyes of 21 patients were analysed. The mean patient age was 67·0 (11·5) years; 14 patients were female, seven were male.

The mean iridotomy area prior to pupil dilatation was 0·075 (0·055) mm^{-2}. The mean iridotomy area following pupil dilatation was 0·073 (0·070) mm^{-2} (Student's *t* test not significant). The area of nine iridotomies became larger when the pupil was dilated, 11 became smaller and one remained unchanged. The mean percentage change in iridotomy area was 96·7 (63·6%) (range 11–233%). Iridotomy area following pupil dilatation correlated with iridotomy area prior to pupil dilatation ($r=0·815$, $p<0·01$), but did not significantly correlate with any other measured factor.

In two eyes the iridotomy area was reduced to less than 20% of its initial area (Fig 1). These eyes had a small initial iridotomy area (0·027 and

Figure 2 (A) Effect of pupil dilatation on iridotomy shape. Pupil undilated. Elliptical iridotomy, area 0·151 mm^{-2}. (B) Effect of pupil dilatation on iridotomy shape. Pupil dilated. Circular iridotomy, area 0·227 mm^{-2}.

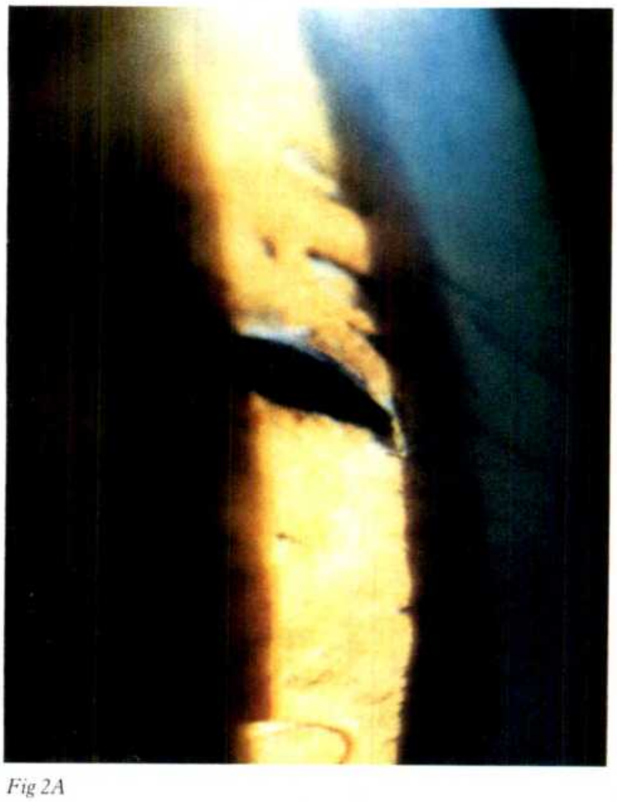

Fig 2A

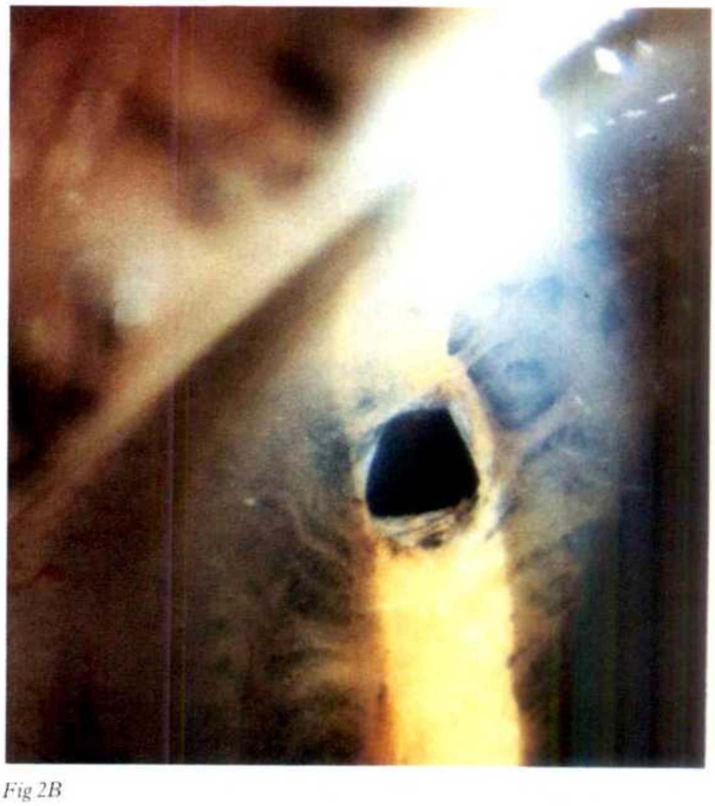

Fig 2B

0·031 mm^{-2}), but no other factor was identified which might have predicted reduction of iridotomy area on pupil dilatation.

The cornea and iris approximated to a circle in every case, and diameter was used to calculate area. The area of the iris before and after pupil dilatation could be obtained from the difference between the area of the cornea and the area of the pupil. The mean iris area following pupil dilatation was 75·8 (11·1)% of that prior to pupil dilatation. Change in iris area did not correlate with change in iridotomy area on dilating the pupil.

With the pupil undilated every iridotomy was elliptical, with the long axis radial to the limbus. On dilating the pupil the iridotomy shape changed. Twelve iridotomies became elliptical with the long axis circumferential to the limbus, three iridotomies became circular, and six remained elliptical with the long axis radial to the limbus. The radial diameter/circumferential ratio was termed the 'ellipse ratio'. The mean iridotomy ellipse ratio prior to pupil dilatation was 3·0 (2·3), and the mean iridotomy ellipse ratio following pupil dilatation was 1·14 (0·82). An ellipse ratio of 1·0 would describe a circle.

Change from an elliptical shape to a more circular shape might be expected to increase area, as in Figure 2. However there was no significant correlation between the change in iridotomy area on pupil dilatation and the ellipse ratio of the iridotomy prior to pupil dilatation, the ellipse ratio of the iridotomy after pupil dilatation, or the change in ellipse ratio on pupil dilatation.

The mean distance of the nearest point of the iridotomy to the limbus prior to dilating the pupil was 1·08 (0·43) mm. The mean distance of the nearest point of the iridotomy to the limbus after dilating the pupil was 0·60 (0·43) mm. There was no significant correlation between the change in iridotomy area on pupil dilatation and the distance of the nearest point of the iridotomy to the limbus before or after dilating the pupil.

Discussion

Several factors may contribute to the reduction in area of an iridotomy of theoretically 'safe' area below that needed to prevent acute angle closure glaucoma. Most cases of acute angle closure glaucoma following Nd:YAG laser iridotomy have occurred within 1 month of treatment. Naveh has observed rapid diminution of Nd:YAG laser iridotomy area within 1 hour of treatment in six eyes.[12] In each case a return to the original area occurred within 2 weeks. Localised iris oedema around the treatment site may have been responsible.

Re-closure of Nd-YAG laser iridotomies owing to iris pigment epithelium proliferation is unusual, and tends to occur 1–4 months following treatment.[3 4 12–14] Re-closure resulted in acute angle closure glaucoma in two eyes reported by Wishart,[13] and one eye reported by Gray.[3]

Provocation tests have not been helpful in identifying eyes at risk, as eyes which developed acute angle closure glaucoma following Nd:YAG laser iridotomy did so before a provocation test had been performed.[3 13]

Our findings indicate that iridotomies may become reduced to less than 20% of their initial area following pupil dilatation. Changes in iridotomy area following pupil dilatation are unpredictable, and the only factor we could identify which correlated with iridotomy area following dilatation was iridotomy area prior to dilatation. It would appear that the only effective method to preventing unacceptably small iridotomy area following pupil dilatation is to create a sufficiently large iridotomy at the time of initial laser surgery. We have previously postulated that an iridotomy should be at least 200 μm in diameter (0·031 mm^{-2} area if circular) in order reliably to prevent the development of angle closure glaucoma,[9] and we continue to suggest that this figure is used as a guideline for treatment.

This study was supported by a grant from the WH Ross Foundation.

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Closing Date: 30 November 1992

British Journal of Ophthalmology 1992; 76: 681–684

MINI REVIEW

Pharmacokinetics of ophthalmic corticosteroids

Corticosteroids have been used by ophthalmologists with increasing frequency over the past 30 years, with the concomitant development of a diverse range of drop, ointment, subconjunctival, and oral preparations. Though the clinical benefits and side effects of such corticosteroid preparations have been well documented, their basic pharmacokinetics in the human eye have yet to be fully established. Indeed most of our pharmacokinetic knowledge of these drugs has been elucidated by extrapolation of data obtained from rabbit experiments.[1–26] These results can be significantly disparate from human data because of the thinner rabbit cornea, lower rabbit blink rate, effect of general anaesthetic, upright or recumbent position, vascularity of the rabbit orbital plexus, and small rabbit body mass.[18 27–29] Thus, in general, measurements of steroid concentration in rabbit eyes[2 7 13 19–21 24 25] tend to be significantly higher than those recorded in humans.[30–35]

Topical ophthalmic drops/ointments

These are still the most common methods of administering steroids to the eye and following a single topical drop, steroid is measurable in human aqueous humour within 15–30 minutes.[30–32] Not surprisingly, increased steroid concentration in topical preparations generally results in higher intraocular concentrations,[13 14] but for prednisolone acetate the optimum dose response effect in experimental keratitis occurs at a 1% concentration, and is not improved by further increases in concentration.[20] Increasing ocular contact time by preparing topical steroids in a microsuspension,[25] gel, or viscous formulation[35 36] can double the corneal and aqueous humour concentrations of steroid compared with the same drug applied as a solution.[13 35 36] Other apparently minor changes in formulation, such as the addition of benzalkonium, can significantly alter the pharmacokinetics of topical steroids.[13] For these reasons many workers chose to use commercially prepared 'off the shelf' steroids in an attempt to unravel differences in pharmacokinetic behaviour, which may be associated with clinical efficacy.[17 21 26 30–34 37] In contradistinction, the preparation of different topical steroid derivatives in an identical base vehicle has demonstrated that the greatest barrier to intraocular penetration is the lipid rich corneal epithelium, which retards the ingress of polar, hydrophilic derivatives such as prednisolone phosphate,[9 12 16] but is much less of a barrier to lipophilic derivatives such as the alcohol and acetate forms of dexamethasone and prednisolone.[15 16 20 26 38] Interestingly, if this epithelial barrier is removed prednisolone phosphate penetrates the cornea in much higher quantities than the lipophilic, acetate derivative.[12] These additive effects of increased concentration, lipophilic derivation, and the increased contact time afforded by a microsuspension have been demonstrated in humans, where a single drop of prednisolone acetate 1·0% microsuspension has been shown to produce intraocular steroid concentrations which were 20-fold those of a single drop of prednisolone phosphate 0·5% solution,[31 33] and almost 100-fold those of a single drop of betamethasone phosphate 0·1% solution.[32] In contrast, when dexamethasone, prednisolone, and fluorometholone are all formulated at a concentration of 0·1% in an identical vehicle, the aqueous humour concentrations of these steroids are almost identical.[19] None the less it is essential when considering such empirical data, to recall that the systemic anti-inflammatory effect of both betamethasone and dexamethasone is five to seven times that of prednisolone.[39 40] The local anti-inflammatory potency of ocular steroids has yet to be fully investigated and whilst early work suggested that prednisolone acetate 1% had the greatest anti-inflammatory effect in experimental keratitis,[17] later studies demonstrated that fluorometholone acetate in a 1% formulation was equally efficacious in the same model.[26] However, prednisolone acetate 1·0% drops have been shown to significantly inhibit the tear film polymorphonuclear leucocyte response to partial denudation of the corneal epithelium, whereas 0·1% concentrations of prednisolone acetate, dexamethasone, and fluorometholone are ineffective.[37] As already noted, the absence of corneal epithelium can significantly affect the penetration of topical steroids, and it may also be relevant to the clinical situation that higher corneal concentrations of steroid may occur in the presence of intraocular inflammation,[9] whereas the concomitant application of an antibiotic drop within 60 seconds of steroid application can reduce the bioavailability of the applied steroid by almost 70%.[23] It has not been established which concentration of steroid is desirable for minor ocular inflammatory conditions such as postoperative uveitis, and whilst concentrations of 670 ng/ml of prednisolone have been recorded in human aqueous humour,[33] perhaps a peak of 25 ng/ml[31] might be sufficient to suppress inflammation and minimise side effects.[41] For comparison, peak timolol concentrations of 2500 ng/ml have been recorded in rabbit aqueous humour following topical application, yet β receptor blockade can be obtained by as little as 9 ng/ml.[42]

Preparation of prednisolone acetate as a gel provides a more prolonged release[43] and higher peak aqueous concentration when compared with an equivalent topical solution.[24] However, some viscous agents and ointments may actually produce lower peak ocular concentrations of steroid when compared with drops.[12 43] Despite this, owing to prolonged release, a single application of a steroid ointment such as dexamethasone phosphate results in only 25% less overall absorption of steroid than a single drop of the same steroid.[12]

It is generally believed that most of the topical and, indeed, subconjunctival steroid (see below), enters the eye via the cornea, thus radiolabelled hydrocortisone produces only 2·5% of the anticipated aqueous humour concentration when corneal penetration is prevented, compared with topical application with free access to the cornea.[44] However, for other drugs such as pilocarpine and timolol, penetration into the iris and ciliary body via the non-corneal route may account for drug concentrations which reach almost 10% of the combined corneal and non-corneal route,[44 45] and such trans-scleral penetration may be even more important for larger molecules, such as inulin.[45]

Periocular injections

Repeated subconjunctival injections of prednisolone (50 mg) have been shown to be inferior to hourly topical prednisolone acetate 1% drops (6·5 mg) in reducing the inflammatory response in experimental keratitis.[22] Early analytical techniques suggested that such subconjunctivally injected steroid entered the eye via the sclera.[5] Indeed, the sclera is readily permeable to even relatively large molecules such as albumin,[46] and therefore, not surprisingly, high levels of corticosteroid can be detected in the sclera underlying a subconjunctival injection site.[5] However, the greater concentration of such steroid appears to enter the eye by diffusing through the puncture site in the conjunctiva into the tear film, and thence via the cornea into the intraocular milieu.[14]

In this context it is not unexpected that sub-Tenon's injections of methyl prednisolone in monkeys produced significant anterior segment steroid concentrations (approx 25 ng/ml) but could only produce peak vitreous concentrations of 2 ng/ml.[47] In contrast, retrobulbar methyl prednisolone in the same model produced much higher posterior uveal/retinal concentrations and significant vitreous levels which persisted for up to 9 days.[48] These discrepancies might be partly explained by the lack of post-equatorial diffusion of drug following subconjunctival and sub-Tenon's injections.[29] It is notable that, in contrast to the enhanced corneal penetration of topical steroid drops previously noted in intraocular inflammation, when a peribulbar injection is used, total ocular steroid levels may actually be lower in eyes with intraocular inflammation compared with uninflamed eyes.[29]

The inherent risks of peribulbar injection of steroid (see below) and the availability of alternative, superior methods of application, suggest to the author, in the context of the preceding data, that the role of peribulbar injection is limited to the operating room and to a few other selected situations where frequent topical medication is not practicable. The short term local use of orbital floor steroids in non-necrotising scleritis may be such an exception to this,[49] whereas the role of retrobulbar steroid in the treatment of persistent macular oedema remains unresolved.[50]

Systemic administration

When one considers the bodywide distribution of a systemically administered steroid, it is easy to comprehend the dramatically larger steroid doses required to equal the previously noted aqueous humour concentrations produced by topical drops; however, the extent of this disparity is seldom fully appreciated. In the rabbit it has been shown that an intravenous dose of 25 mg dexamethasone (equivalent to 500 mg in a 70 kg man!) was required to produce aqueous humour levels which were comparable with those achieved following topical dexamethasone alcohol drops, whereas a similar intravenous dose of prednisolone only achieved 50% of the peak aqueous concentration obtained by four drops of methyl prednisolone 0·5%.[2] Similarly, intramuscular methyl prednisolone in squirrel monkeys produced total ocular tissue concentrations, and vitreous concentrations in particular, which were less than 1% of those obtained by a similar dose given as a periocular injection.[48] Indeed, maximal intraocular steroid concentration may actually represent as little as 0·5% of an intravenous dose.[29] That systemic steroids have an important role in ophthalmic practice, such as the treatment of corneal graft rejection,[51] is not in question, but they must be used in the knowledge that they act by primarily affecting the systemic limb of ocular disease and that there are superior, local, alternative methods of producing significant intraocular concentrations of steroid, if that is what is desired.

Collagen shields and contact lenses

Waltman and Kaufmann demonstrated that hydrophilic contact lenses could be presoaked in a drug solution and used as a form of delayed release vehicle.[52] A few years later Hull *et al* established that hydrophilic contact lenses, presoaked in 1% prednisolone phosphate, produced an aqueous humour peak concentration that was three to fourfold that obtained by application of topical drops and this advantage was maintained at 4 hours.[53] The search for a topically applied, slow release drug system in other areas led to the successful development of pilocarpine ocuserts, which though not widely used, and despite some limitations, have been shown to be a viable alternative to topical drops in certain patients.[54]

Similarly, early soluble collagen inserts presoaked in gentamicin produced higher tear film and corneal concentrations of gentamicin than gentamicin administered in drop, ointment, or subconjunctival form.[55] The development of dissolving collagen shields has rekindled interest in this method of delivering ophthalmic drugs and such shields presoaked in tobramycin have been well tolerated by patients[56] and have been shown to produce higher aqueous and corneal concentrations of tobramycin than subconjunctival injections.[57] Collagen shields have also been suggested as the optimum vehicle for poorly soluble drugs such as cyclosporin.[58] Recently it has been demonstrated that collagen shields presoaked in dexamethasone alcohol produce superior intraocular concentrations of dexamethasone than hourly drops over the first 4 hours, and that a combination of a presoaked shield and hourly topical drops doubles the cumulative delivery of steroid to the eye at 6 hours when compared with hourly drops alone.[59] For those looking for the ideal short term sustained release vehicle, and a safe yet superior alternative to subconjunctival injections, collagen shields would appear to provide increased compliance, better 24 hour control, higher ocular drug concentrations than comparable methods of administration, and good patient tolerance. However, like pilocarpine ocuserts they have yet to gain wide acceptance by clinicians and whether, like ocuserts, they will fail to gain a regular place in our pharmacological armamentarium, owing to limitations yet to be identified, remains to be seen. In a note of caution, it has already been highlighted that certain antibiotic and steroid combinations in collagen shields may provoke adverse corneal reactions.[60]

Intravitreal injection, liposomes, and iontophoresis

Whilst intravitreal injections of antibiotics have become a standard technique in the treatment of endophthalmitis the use of intravitreal steroids in ophthalmology is less well established. Ocular dialysis has demonstrated that after subconjunctival gentamicin, virtually no gentamicin is recorded in the vitreous, whereas intravitreal injection of gentamicin may produce significant levels with a half life of up to 22 hours.[61] In contrast, intravitreally injected dexamethasone appears to have a half life of 3 hours with only 10% of the peak concentration remaining at 8 hours, although concentrations of 50 ng/ml may persist for up to 4 days.[62]

The incorporation of drugs into liposomes has demonstrated an up to 10 times improvement in the intraocular penetration of hydrophilic drugs following topical application.[63] However, possibly because the commonly used ophthalmic steroids such as dexamethasone alcohol, prednisolone acetate, and fluorometholone are already lipophilic, there has, as yet, been little utilisation of liposome delivery for steroids. Transcorneal and trans-scleral iontophoresis of polar drugs, which normally penetrate these structures poorly, remain largely experimental, though the trans-scleral iontophoresis of dexamethasone phosphate can produce higher vitreous concentrations than the retrobulbar, subconjunctival, or topical routes.[64]

Side effects of ophthalmic steroids

The adverse effects of systemic steroids are well known to ophthalmologists, therefore local administration is often seen as a logical method of minimising such side effects.[49] Some local applications are not without obvious inherent risks such as bulbar perforation, choroidal injection, central retinal artery occlusion, muscle imbalance and persistently raised intraocular pressure following the periocular injection of steroids.[65-67] Additionally, systemic absorption of periocular steroids in rabbits has been noted to decrease circulating lymphocytes and antibodies,[27] and to reduce the total white blood cell count.[22] Surprisingly, considering the small volume of steroid administered, topical drop application of steroid in rabbits produces significant liver, urine, and plasma concentrations[36] and by 30 minutes almost a third of the applied steroid is distributed systemically,[3] with less than 5% of the administered steroid being recoverable from the eye.[3,9] Owing to this significant systemic dissemination of steroid, topical application inhibits corneal wound healing in both the treated and the untreated, contralateral eye in rabbits.[28] In larger experimental animals, following eight drops of prednisolone acetate 1·0% per day (4 mg of prednisolone per day), both small dogs[68] and large dogs (27–41 kg)[69] have exhibited adrenal suppression, though the adrenal axis is more readily suppressed in dogs than in humans.[68,69] In humans, the systemic absorption of topically applied drugs such as β blockers is well established,[70] whereas the systemic effects of topical ocular steroids is less clearly defined, and whilst Burch[71] observed a 50% decrease in endogenous steroid production in male volunteers given hourly dexamethasone 0·01% drops (0·75 mg dexamethasone per day) for 6 days. Krupin[72] demonstrated a reduction in endogenous plasma cortisol but no adrenal axis suppression following eight drops of dexamethasone 0·1% per day for 6 weeks. It seems reasonable, therefore, to suggest that the possibility of adrenal suppression should be considered when ophthalmologists employ intensive topical steroids such as prednisolone acetate 1·0% and dexamethasone 0·1%.

Conclusion

Although more information on ophthalmic steroids in humans is becoming available, we still rely heavily on data derived from animal models. Fortunately, while some of the animal data are conflicting, the general trends appear to be similar in humans, though the magnitude of intraocular steroid penetration in humans appears less. The marked differences in pharmacokinetic behaviour illustrated by identical concentrations of the same steroid, in different topical drop formulations, does mean that generic equivalence cannot be assumed between preparations merely on the basis of equivalent steroid content. Topical and local application of steroids appears preferable to systemic administration wherever possible; however, the limitations of, and alternatives to, subconjunctival injection should be carefully considered, as should the possibility of adrenal suppression following intensive ophthalmic corticosteroid drops in children and small adults.

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CASE REPORTS

A case of amniotic band syndrome with bilateral epibulbar choristoma

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Abstract

An autopsy case of amniotic band syndrome with bilateral epibulbar choristoma is described. The left eye reveals a complex choristoma and the right eye a dermis-like choristoma. Both choristomatous lesions included lenticular tissue suggesting that rupture of the amnion, which is the initial event of amniotic band syndrome, might have occurred at about the fourth week of gestation. Since the other systemic manifestations of amniotic band syndrome are considered to be compression deformities of the fetus caused by oligohydramnios or amniotic band, the occurrence of epibulbar choristomas in both eyes in this case suggests that a compression mechanism may play a role in the pathogenesis of epibulbar choristoma.

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Early rupture of the amnion, leading to oligohydramnios and formation of the amniotic constrictive band, is considered to be the initial event of amniotic band syndrome, resulting in compression deformities of the fetus. The manifestation of intrauterine compression, such as amputation of the extremities and digits, craniofacial clefts that often do not correspond in location to disturbances in normal embryogenesis, are diagnostic of amniotic band syndrome.[1] Ocular tissue may also be involved. Common ocular manifestations are congenital or acquired corneal opacity, ectropion, coloboma of eyelid, microphthalmos, strabismus, and hypertelorism.[2-4] BenEzra *et al*[5] reported a case in which a uveal coloboma was probably caused by an amniotic band that had lodged in the fetal fissure and prevented the closure. We describe an autopsy case of amniotic band syndrome which presented with corneal opacity, ectropion, and coloboma of the eyelid, as well as other systemic deformities. We report the histological features of the globes and eyelids of this uncommon malformation.

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Case report

A 28-year-old Japanese woman gave birth to a 565 g female neonate at 25 weeks of gestation by spontaneous vaginal delivery. The woman had aborted twice and this pregnancy was complicated by an ultrasonographically suggested acrania probably due to amniotic band syndrome. Ultrasonography demonstrated oligohydramnios and adherence of the head of the fetus and the placenta. The level of α fetoprotein was elevated both in the maternal serum (2034 μg/l) and the amniotic fluid (238 480 μg/l; normal level >20 μg/l). The Apgar score was 0 at 1 minute and the neonate could not be

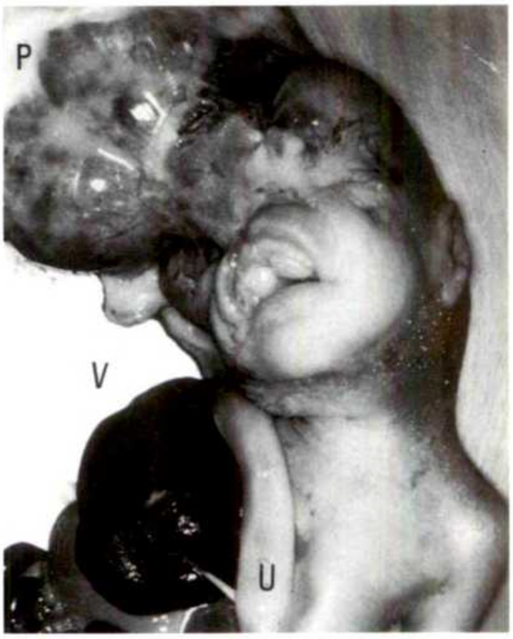

Figure 1 The scalp of the fetus and amnion merge at the supraorbital region and the head is attached to the placenta. P=placenta; U=umbilical cord; V=viscera.

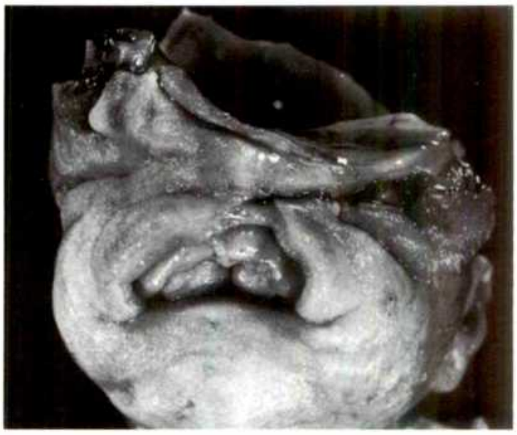

Figure 2 The face of the fetus. Placenta and brain were removed. Left eye reveals ectropion and coloboma of the lower lid. The right eye shows that the palpebral fissure is scarcely open.

resuscitated because of extensive craniofacial deformities.

A fibrous band was attached to the scalp of the fetus and inspection revealed multiple malformations. The skull bones were incompletely formed and brain tissue was exposed. The scalp was contiguous with the amnion so the head of the fetus was attached to the placenta. Other systemic abnormalities were as follows: abdominal and right thoracic wall defects, coarctation of the aorta, amputation of the third and fourth fingers of the left hand, amputation of the first, second, fourth, and fifth toes of the left foot, facial cleft, scoliosis, and short umbilical cord (Fig 1).

Other malformations observed by inspection were as follows: right eye, the palpebral fissure was so narrow that the right globe was obscured; left eye, ectropion and coloboma of the lower eyelid were present. An opaque cornea-like structure was observed and was contiguous with upper eyelid, causing incomplete formation of the upper conjunctival fornix (Fig 2).

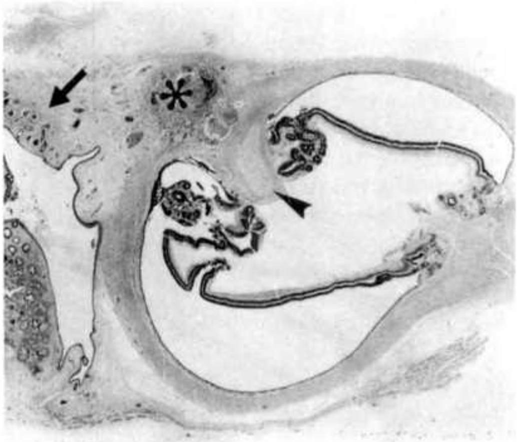

Fig 3A

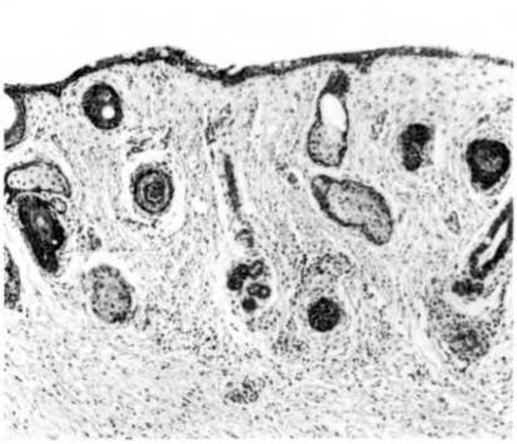

Fig3B

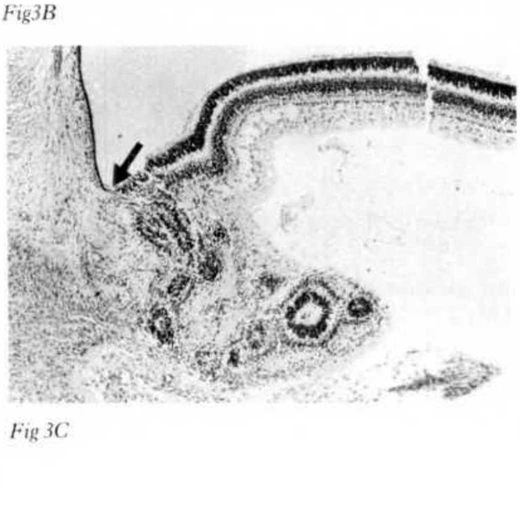

Fig 3C

Figure 3 (A) Right globe and eyelids. The anterior segment is replaced by fibrous tissue containing cartilage (arrowhead), lenticular tissue (asterisk), and skin appendages (arrow) (haematoxylin and eosin, ×2·5). (B) The anterior segment of right eye. The fibrous tissue includes skin appendages (haematoxylin and eosin, ×150). (C) The retina with dysplastic changes showing rosette formation lying directly on the sclera. Retinal pigment epithelium fails to reach optic disc (arrow) (haematoxylin and eosin, ×100).

Histopathology

RIGHT EYE (FIG 3A)

Both the upper and lower eyelids were well formed showing eyelashes, the extraocular muscles, and tarsus composed of collagenous fibres including Meibomian glands. The cornea, anterior chamber, and iris were replaced by dermis-like connective tissue including rudimentary lens, cartilage, hair follicles, and pilosebaceous units. This lesion was covered with stratified squamous or cuboidal epithelium (Fig 3B). The posterior segment was almost normal except for the dysplastic retina showing rosette formation. The pigment epithelium did not reach the optic disc resulting in the dysplastic retina lying in direct contact with the sclera, suggesting an incomplete closure of the fetal fissure. The hyaloid artery was observed (Fig 3C).

LEFT EYE (FIG 4)

The left eye showed similar histological findings to those of the right eye except for minor

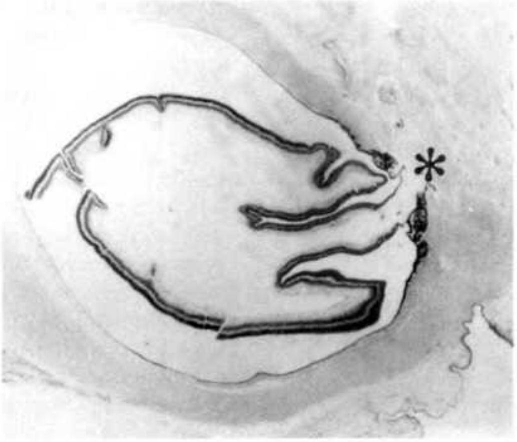

Fig 4A

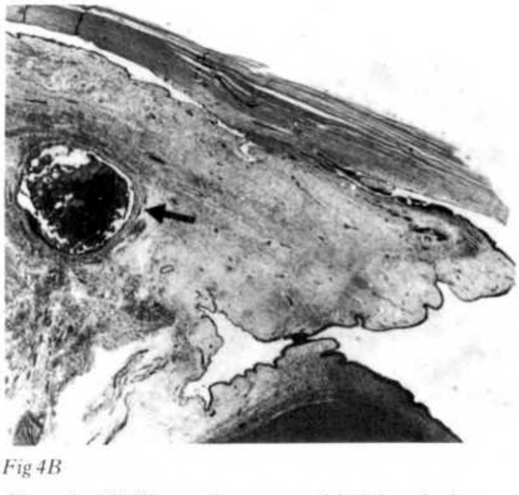

Fig 4B

Figure 4 (A) The anterior segment of the left eye is also replaced by fibrous tissue (asterisk) (haematoxylin and eosin, ×2·5) (B) The fibrous tissue includes lenticular tissue (arrow), but no skin appendages (haematoxylin and eosin, ×100).

differences. The lower eyelid was well formed but the upper eyelid was rudimentary. The cornea, anterior chamber, iris, and ciliary body were replaced by fibrous connective tissue (Fig 4A). This connective tissue was covered with stratified squamous epithelium and included islands of lenticular tissue, but no other components such as skin appendage and cartilage were found (Fig 4B). The posterior segment was generally unremarkable.

Discussion

The incidence of amniotic band syndrome has been estimated at one in 5000 to 15 000 live births. Deformities observed in amniotic band syndrome have been considered to be compression deformities caused by the amniotic band or amnion itself[6]; the orbit or globe may be involved.

Epibulbar choristomas can be divided into four main histopathological groups; dermoid, lipodermoid, single tissue choristoma, and complex choristoma.[7] A dermoid consists of dermis-like connective tissue in which pilosebaceous units are present. When the lesion consists of dermis-like connective tissue and no pilosebaceous units it is termed a dermis-like choristoma, belonging to single tissue choristoma.[8] Complex choristomas consist of two or more choristomatous tissues.[7] In the left eye of the present case, the cornea, anterior chamber, and iris were replaced by choristomatous dermis-like connective tissue covered by stratified squamous epithelium with hair follicles, pilosebaceous units, and a cartilaginous tissue. From these findings the left eye was diagnosed as an epibulbar complex choristoma. The right eye of the present case showed similar histological findings to those of left eye. The cornea, anterior chamber, and iris were replaced by choristomatous dermis-like connective tissue covered with stratified squamous epithelium. Since no other choristomatous component could be found the right eye was diagnosed as dermis-like choristoma.

In both eyes alterations in the posterior segment were milder compared with the anterior segment. In the left eye focal dysplastic changes of the retina showing rosette formation were seen. We have previously reported two cases of corneal choristoma and both of them showed similar retinal dysplastic change.[8] In both eyes lenticular tissue is intermingled in the choristomatous tissue, suggesting that the malformation of the eye occurred during formation of the lens at about the fourth week of gestation,[9] and that the rupture of the amnion in this case happened at about the same time or before.

There is no satisfactory explanation of the origin of the epibulbar choristoma.[10] Ozanics[11] suggested that many congenital malformations of the anterior segment of the eye probably arose from derangement in the migration of neural crest cells. The case described here could present evidence to support this theory because the choristomatous tissue consists of cartilaginous and fibrous tissues which are derivative of neural crest cells. So the fact that this case of amniotic band syndrome had epibulbar choristoma in both eyes might indicate that a compression mechanism could play a role in the pathogenesis of epibulbar choristoma by disturbing the migration of the neural crest cells into the optic cup.

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Periocular migration of an intraocular lens

C Jenkins

Abstract

A woman presented with a painful eye 6 weeks after cataract extraction and intraocular lens implantation. In the past she had had a sector iridectomy for iris bombé caused by chronic anterior uveitis. On examination the three central corneal sutures were absent, whilst the medial and lateral sutures had broken and were protruding from the section. The eye was quiet and the section intact. Combined clinical and ultrasound examination failed to locate the intraocular lens. Four months postoperatively, while being fitted for contact lenses for the correction of aphakia, the intraocular lens appeared from the superior fornix.

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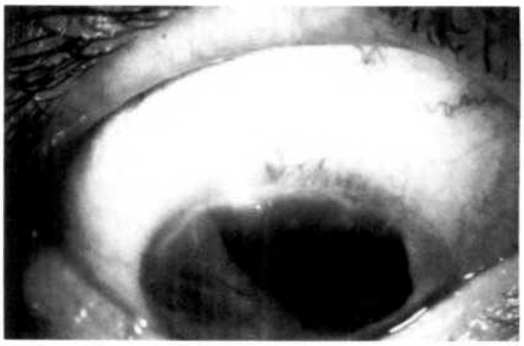

Figure 1 The spontaneously sealed corneal section is shown. Note the absence of conjunctival injection and the presence of a broad iridectomy.

A recent report[1] documented six cases of periocular migration of hard contact lenses. The authors stated that this phenomenon was not particularly unusual despite being largely unreported. A rather more unusual case is reported here. The patient had been referred to the contact lens department in order to correct aphakia. At the second contact lens fitting, 4 months after cataract extraction, an intraocular lens unexpectedly appeared from under the upper fornix.

Case report

A 49-year-old woman presented to the accident and emergency department 6 weeks following a right cataract extraction and implantation of a posterior chamber intraocular lens (IOL). She gave a 5 day history of watering and a foreign body sensation in the right eye.

She had a long history of bilateral chronic granulomatous anterior uveitis dating from 1976 which had for several years required treatment with oral prednisolone. In 1980 she developed iris bombé with a rise in pressure for which broad iridectomy was performed. For 10 years she remained symptom free, but re-presented in June 1990 with a further flare up of uveitis. At this stage the vision in her right eye was 3/60, which was thought to be mainly due to a large posterior subcapsular cataract. Eventually in August 1991 a right cataract extraction was carried out under local anaesthesia. There were dense adhesions between the pupil and lens inferiorly and the operation was complicated by zonule rupture superiorly with prolapse of vitreous. An anterior vitrectomy was performed through the area of zonule dehiscence and a 20·5 dioptre one-piece IOL with angled haptics was inserted into the ciliary sulcus without further complication. Two days postoperatively the IOL was noticed to be decentred superotemporally where it remained on review at her first postoperative visit 1 week later. At this stage the right visual acuity was <6/60 unaided, 3/24 with a pinhole. There was some posterior capsular opacification and probable macular oedema.

When examined in the accident and emergency department the visual acuity in the right eye was 2/60. The three central sutures were missing and the most medial and lateral were protruding out of the section, which itself was secure – the Seidel test being negative. Figure 1 shows the corneal wound after removal of the sutures. The conjunctiva was not inflamed, and the cornea was clear with old keratic precipitates. There were only a few cells in the anterior chamber. Vitreous was in the anterior chamber but not adjacent to the section. The posterior capsule was absent. There were a few pigmented cells in the vitreous, and the retina was flat with slight macular and disc oedema. The intraocular pressure (IOP) was 16 mm Hg. An ultrasound examination was performed which failed to locate the IOL. Three months postoperatively the patient was referred to the contact lens department for the fitting of a contact lens. She was able to see 6/36 with the aid of a +11·5D lens. One month later she was re-examined. On both occasions her upper eyelid had been everted without comment, but during the course of instruction to remove her contact lens the missing intraocular lens re-appeared (Fig 2).

Discussion

While cases of missing contact lenses reappearing from under the upper eyelid are by no means rare, I believe this is the first reported case involving an intraocular lens. I also believe it to be the first reported case of a self-sealing wound following IOL expulsion. The patient initially presented to a bemused casualty officer with three sutures missing, two broken sutures, no IOL, and a quiet eye despite her long-standing previous history of uveitis. Despite repeated examination and sophisticated ultrasound imaging, it was assumed that the lens lay adjac-

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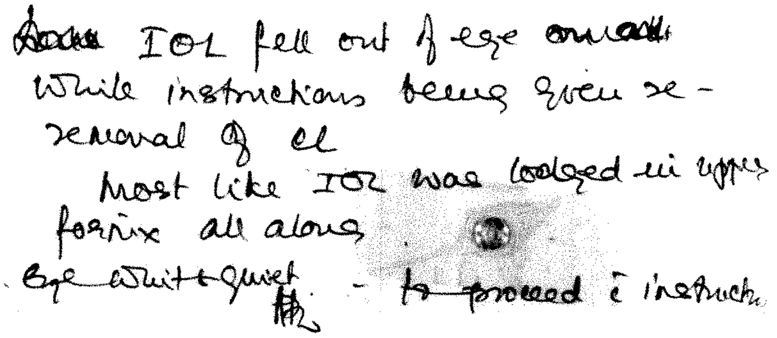

[illegible] IOL fell out of eye [illegible]
While instructions being given re-
removal of el
Most like IOL was lodged in upper
fornix all along
Eye white + quiet – to proceed c̄ instruct.

Figure 2 Photograph of a page from the notes showing the expelled intraocular lens.

ent to the pars plana and ciliary body. Eyelid eversion in the presence of an incompletely healed wound was not attempted and the location of the missing implant high in the superior fornix was not detected.

Unusual features of the case were the self-sealing wound and the absence of attendant intraocular inflammation. It is recognised that, in the presence of even partial rupture of the posterior capsule, the lens position may be more unstable. The implant was noted to be decentred superiorly 1 day postoperatively. Furthermore, a broad iridectomy had previously been performed, so that when the intraorbital pressure was raised during a bout of vomiting expulsion of the IOL occurred.

Dislocation of a posterior chamber lens relative to its normal position behind the iris is one of many complications of cataract surgery. It may rarely fall backwards into the posterior chamber. More frequently, the pupil margin is caught behind the implant resulting in gross distortion of the pupil shape. One of the most unusual complications is expulsion of the implant. This almost always occurs in the context of obvious ocular trauma and is associated with other signs of ocular injury. For example, in a previously reported case of posterior chamber lens expulsion, blunt trauma in the form of a dog paw was cited. This case was associated with vitreous prolapse and retinal detachment.[2]

The case reported above was unusual for both the expulsion of the IOL and the lack of ocular inflammation. The subsequent location of the implant in the superior fornix was extraordinary!

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Colour Doppler ultrasound in the management of a case of cranial arteritis

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Abstract

Colour Doppler ultrasound allows simultaneous B scan and Doppler imaging and can be employed to determine the velocity of blood flow in the vasculature of the eye and orbit. We describe a case of cranial arteritis (giant cell arteritis) in which serial velocimetry recordings were obtained. At one stage in the disease process no blood flow was detectable in the orbit despite previously reliable recordings. This coincided with a deterioration of the clinical state of the patient as signified by recurrent anterior ischaemic optic neuropathy despite controlled symptomatology and erythrocyte sedimentation rate by prednisolone therapy. Subsequent increase in the immunosuppressive therapy was accompanied by a return of blood flow in the orbit. Colour Doppler ultrasound may prove to be a useful examination technique in the diagnosis and management of cranial arteritis.

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Colour Doppler velocimetry has been described in the examination of the blood flow in the orbit.[1] The technique has been more fully evaluated recently,[2,3] and used in the examination of patients with carotico-cavernous fistula[4] and malignant melanoma of the uvea.[5] We describe a case of cranial arteritis in which blood velocity measurements in the orbit changed with the course of the disease providing useful information which directly affected the management of the patient.

Case report

A 74-year-old female presented with jaw claudication, headache, malaise, and loss of vision in her right eye to counting fingers vision only. She also gave a history of amaurotic attacks in the left eye. Examination showed a pale swollen optic disc on the right side. Her erythrocyte sedimentation rate (ESR) was 132 mm/hour and a diagnosis of cranial arteritis was suspected and later confirmed by temporal artery biopsy. Systemic prednisolone 80 mg daily was begun.

Colour Doppler velocimetry was performed on the right eye. The examination showed blood flow in the ophthalmic artery and its continuation along the medial orbital wall. At the optic nerve head the central retinal artery was detectable but the posterior ciliary arteries were not (Fig 1). Fluorescein angiography showed a normal retinal arteriovenous time of 3·5 seconds with delayed filling of the superior optic disc (6 seconds after the retinal artery) and non perfusion of the inferior disc margin.

After a period of 2 weeks and while still on 50 mg of prednisolone she developed an altitudinal visual field loss from an incomplete anterior ischaemic optic neuropathy in the left eye. This was despite a reduction of the ESR to 8 mm/hour and a symptomatic improvement in her clinical status. At the same time, a repeated colour Doppler ultrasound scan of the right eye showed that the blood flow in the ophthalmic artery was no longer detectable, suggesting further occlusion in this orbit presumably owing to

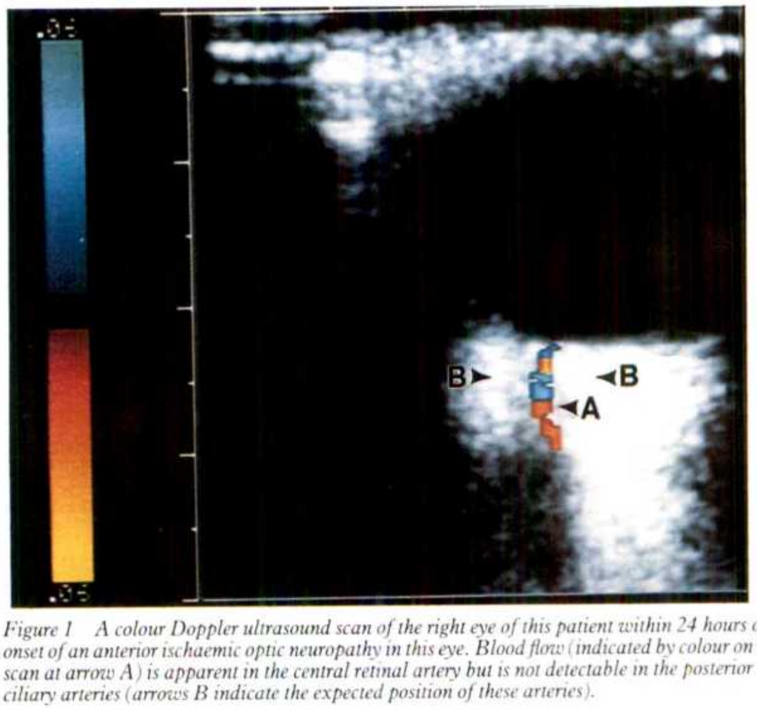

Figure 1 A colour Doppler ultrasound scan of the right eye of this patient within 24 hours of onset of an anterior ischaemic optic neuropathy in this eye. Blood flow (indicated by colour on the scan at arrow A) is apparent in the central retinal artery but is not detectable in the posterior ciliary arteries (arrows B indicate the expected position of these arteries).

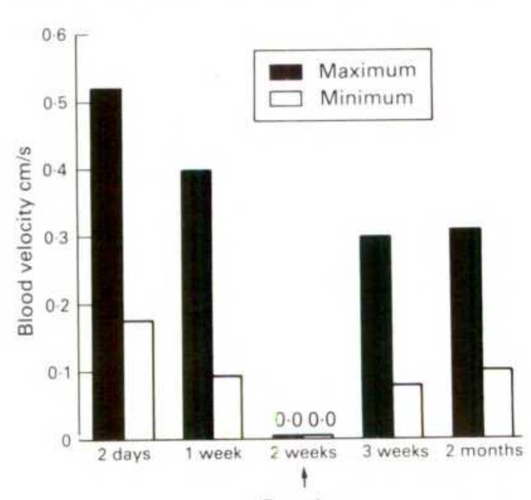

Figure 2 A histogram is shown of five serial measurements of maximum and minimum blood velocity in the right ophthalmic artery. The arrow indicates the time of occurrence of an ischaemic optic neuropathy in the other eye. No colour indices of flow were detected in the right ophthalmic artery.

further active arteritis (Fig 2). The precarious position of the circulation to the left eye was treated by increasing the dose of prednisolone again to 100 mg (with gradual reduction) and with azathioprine 150 mg/day. A repeated temporal artery biopsy confirmed persistent arterial inflammation.

Two months later, while on 35 mg of prednisolone, the patient developed crush fractures of the thoracic spine secondary to osteoporosis. Further reduction of the steroid therapy was, therefore, desirable. Colour Doppler velocimetry was repeated and showed restoration of blood flow in the right ophthalmic artery. In view of this finding the corticosteroid therapy was reduced and no further vascular mishap occurred. The patient is now on a low maintenance dose of corticosteroid and has suffered no further loss in her vision during the ensuing 6 months.

Discussion

Cranial arteritis is a condition which often provides the ophthalmologist with diagnostic and therapeutic difficulties. The arteritis is widespread and yet investigation of the circulation is often restricted to examination of the ocular vasculature detectable by fluorescein angiography. Colour Doppler ultrasound has been shown by the authors[2] and others[3] to be a useful technique in the examination of orbital blood vessels.

In this case the velocimetry of the orbit varied with the clinical condition of the patient. Detectable loss of flow in the ophthalmic artery of the affected side corresponded with the development of an anterior ischaemic optic neuropathy in the second eye and therefore signified ongoing disease despite a reduction in the ESR and symptoms.

We believe that colour Doppler ultrasound will prove to be useful in the diagnosis and management of cranial arteritis. In this case it was used as an investigative aid to the therapeutic management of the patient.

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British Journal of Ophthalmology 1992; 76: 692–693

Complicated extracapsular cataract surgery in pseudoexfoliation syndrome: a case report

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Abstract

Crystalline lens dislocation and zonular dialysis during intraocular surgery are recognised features of the pseudoexfoliation syndrome (PES). A case is reported in which zonular dialysis occurred in both eyes during extracapsular cataract extraction. In particular surgery was complicated by difficulty in performing anterior capsulotomy. Careful preoperative assessment and peroperative technique may help to reduce the risk of surgical complication in PES.

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Pseudoexfoliation syndrome (PES) is characterised by: (1) the presence of grey/white material on the anterior lens capsule and zonule; (2) trabecular meshwork pigmentation; and (3) an association with glaucoma which is usually of the open angle type.

Spontaneous and intraoperative crystalline lens dislocation, zonular dialysis, posterior capsule rupture, and vitreous loss have been described previously in PES. We report a case in which cataract extraction in both eyes was complicated by zonule dialysis.

Case report

In July 1989 a 71-year-old man was referred complaining of a gradual loss of vision in both eyes over 1–2 years. He had also experienced infrequent short lasting episodes of pain in his left eye during this period. There was no other previous ophthalmic history and he was in good general health.

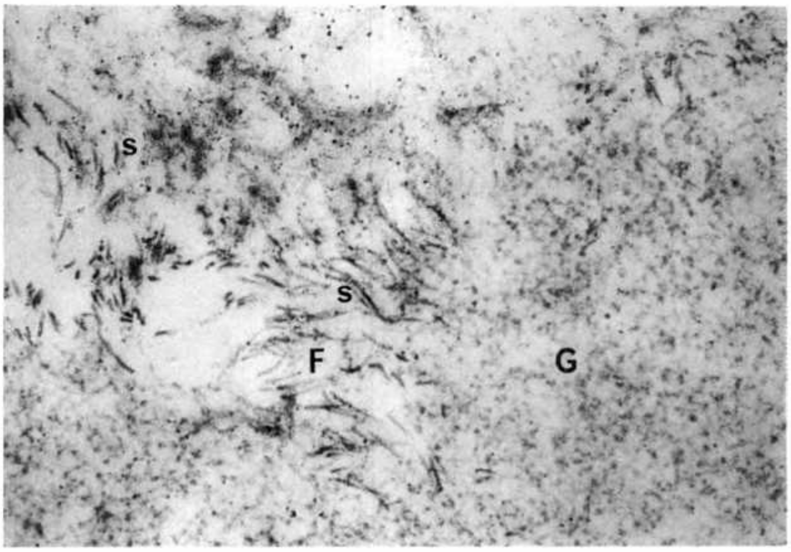

Figure 1 Ultrastructure of pseudoexfoliative material. Both granular (G) and fibrillar (F) components are demonstrated. Note the fine striations (S) which correspond to the 50 nm banded zones in pseudoexfoliation (×34 500).

Visual acuity was 6/24 unaided (6/12 pinhole acuity) in the right eye and hand movements in the left eye. The right eye showed a nuclear cataract and a deep anterior chamber with normal intraocular pressure (IOP). The left eye had a shallow anterior chamber, closed iridocorneal angle, raised intraocular pressure at 31 mm Hg, and a mature cataract. There was pseudoexfoliative material in both eyes.

The patient was admitted for medical control of IOP and then underwent left cataract extraction 3 days after admission. During planned extracapsular surgery the anterior capsulotomy was performed with difficulty owing to the marked toughness of the capsule. After nuclear expression the lens equator was visible inferiorly consistent with a large zonular dialysis. The posterior capsule, soft lens matter, and anterior vitreous were removed using a Kaufmann vitrector. An anterior chamber intraocular lens was inserted. The postoperative course was immediately complicated by raised IOP which was followed by streptococcal endophthalmitis after 48 hours. Despite intensive antibiotic therapy the left eye became painful and blind necessitating evisceration after 2 months.

At follow up after 1 year vision in the right eye had deteriorated to counting fingers and he was readmitted for cataract surgery. At this admission the eye showed increasing nuclear cataract, normal IOP, and there was minimal phakodonesis.

At surgery the lens was quite mobile and capsulotomy proved extremely difficult. It was only possible to make an incomplete canopener capsulotomy with a bent 27 gauge needle which was then augmented with anterior capsule scissors. When using scissors the capsule seemed to be unusually tough. The capsular flap was removed successfully but following nuclear expression there was an inferior zonule dialysis. After administration of chymotrypsin the posterior capsule was removed with forceps (without vitreous loss), peripheral iridectomy was performed, and an anterior chamber intraocular lens was inserted. The postoperative phase was entirely unremarkable and the patient achieved 6/6 vision with suitable refraction. The lens capsule was sent for histological and ultrastructural analysis.

HISTOPATHOLOGY

Light microscopy demonstrated the presence of periodic acid Schiff positive material on the external surface of the lens capsule. The lens epithelium varied from attenuated cells to more cuboidal cells containing cytoplasmic vacuoles. Transmission electron microscopy showed normal capsule appearances in the region where there is no pseudoexfoliative material (PXE). Where PXE material was present on the preequatorial and central disc areas of the anterior capsule there were focal condensations of fibrillogranular material with cross banding at 50 nm and more clearly at 4–5 nm (Fig 1). There appeared to be no other additional pathological features.

Discussion

Spontaneous lens dislocation and complications during both intra and extracapsular surgery in PES have been reported frequently.[1–4] Results from a large series of 2042 eyes undergoing cataract extraction by Naumann *et al* estimate prevalence of PES at 3·5% (72 eyes).[5] The rate of vitreous loss in those with PES was 11·1% compared with 1·6% in those without PES ($p<0·0001$). The incidence of posterior capsule rupture was not significantly different in either group which suggests that vitreous loss was related directly to zonule dialysis rather than capsule weakness. In addition a further series of 977 patients undergoing cataract surgery (241 with PES) reported by Guzek *et al* showed that there was an association between zonular breaks and PES but that there was no increase in the rate of vitreous loss in these patients.[6]

Careful preoperative assessment in PES patients for cataract extraction is essential for avoidance of peroperative complications. Specific signs indicating zonule weakness are lens subluxation, phakodonesis, narrow iridocorneal angle, and anterior chamber asymmetry. Interestingly iridodonesis may well not accompany phakodonesis as the iris appears to have increased rigidity being infiltrated by PXE material.[3 7] This factor may also explain the poor pupillary dilatation in PES patients after mydriatic instillation. Jofe reports that phakodonesis in PES is very difficult to see after pupil dilatation and recommends close examination for phakodonesis prior to dilatation.[8] Angle closure glaucoma as occurred in this case has been attributed to lens mobility[9] but could also be caused by increasing lens size should intumescence develop.

Intraoperative difficulty in cataract extraction in PES patients may be the result of poor pupillary dilatation, excessive lens mobility, iris rigidity, adherence of iris to peripheral lens capsule,[10] difficult nucleus expression, or zonule dialysis with vitreous loss.[3] In our case the most prominent factor causing surgical difficulty was the toughness of the lens capsule in addition to lens movement. The inability of a standard cystotome to perform an adequate capsulotomy and the need for capsule scissors has not been reported. This factor together with zonule laxity was the cause of surgical complication in both eyes.

Histological and ultrastructural findings in this case concur with the reported data on PES.[7] One would expect to find PXE material on the pre-equatorial and central disc areas of the anterior lens separated by a relatively clear band. The PXE material consists of fibres which have a recognisable ultrastructural appearance of cross banding at 4–5 nm and 50 nm and characteristic histochemical properties. The lens capsule was of normal thickness, but it is possible that either the capsule itself becomes tougher in PES or that the deposit of PXE material on the capsule alters the characteristics of the capsule during surgery. If it is presence of PXE material on the iris which contributes to increased rigidity it could have a similar effect on the lens capsule. No other structural abnormality in this case could explain undue toughness of the lens capsule.

The complications described above are relatively common in PES and cases require careful preoperative consideration. Application of the appropriate techniques such as sphincterotomy for small pupils and intracapsular surgery for incipient lens subluxation may be necessary. Where a posterior chamber lens is to be used careful cortical lens matter aspiration and implantation of the lens using viscoelastic agents without dialling is advised. Tarkanen suggests the intentional placement of posterior chamber intraocular lenses in the ciliary sulcus rather than risk strain on a weak zonule.[11] The use of anterior chamber intraocular lenses in patients predisposed to glaucoma carries a risk of further damage to an already compromised drainage angle and may not be advisable.

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British Journal of Ophthalmology 1992; 76: 694–696

Nocardia choroidal abscess

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Abstract

Nocardia is a Gram positive, aerobic, filamentous branching micro-organism that rarely causes human infection. When infection does occur it usually takes the form of a subcutaneous abscess or a pneumonia-like illness. We describe a case of a patient with chronic lymphocytic leukaemia who developed painless loss of vision in the right eye secondary to a choroidal abscess after a prolonged course of treatment on several immunosuppressive agents. The patient also complained of right shoulder pain that was unresponsive to conventional therapy, and had been admitted and treated for several episodes of 'pneumonia'. A diagnostic transvitreal fine-needle aspiration biopsy of the ocular lesion was performed which demonstrated _Nocardia asteroides_. This allowed for appropriate antibiotic therapy to be instituted early in the course of the infection and prompted the systemic work-up which also demonstrated central nervous system and arthropic nocardial infection.

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Nocardia is an aerobic, Gram positive, branching filamentous micro-organism that is found with ubiquity in the soil. Human infection is rare and usually occurs in the form of a subcutaneous abscess or a pneumonia-like illness. Haematogenous dissemination of the organism, particularly in an immunocompromised host, may occur to any organ system and there is a predilection for the central nervous system.[1] We describe a patient with chronic lymphocytic leukaemia (CLL) in whom nocardiosis was initially diagnosed by a fine-needle aspiration biopsy of a choroidal abscess.

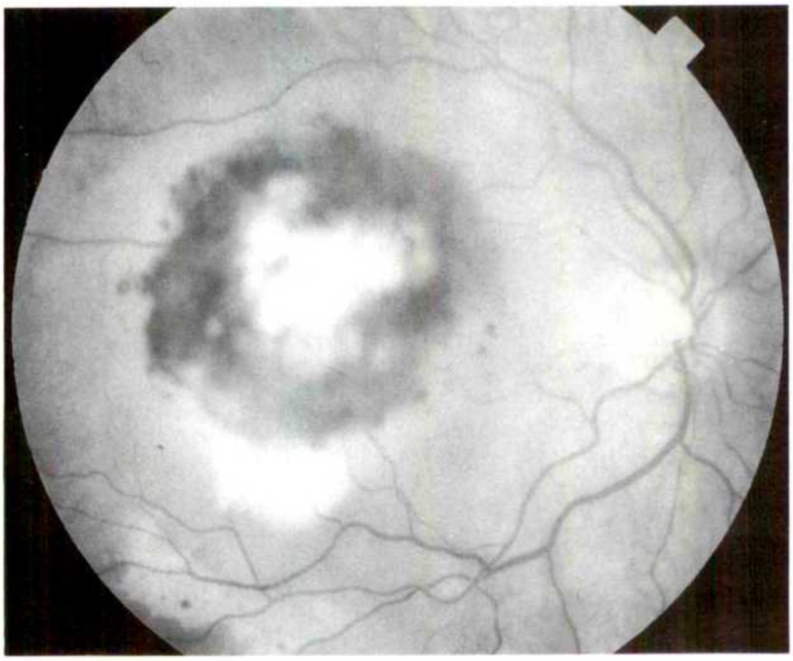


Figure 1 Fundus photograph showing submacular choroidal lesion of the right eye with overlying retinal haemorrhage.

Case report

A 63-year-old white male presented with a 2 week history of painless loss of vision in his right eye. He was diagnosed in 1985 with CLL and had been controlled by several chemotherapeutic regimens, most recently fludarabine and prednisone. He did give a history of several episodes of pneumonia that were believed to be bacterial, and responded slowly to antibiotic therapy. Four weeks before our examination, he developed right shoulder pain that did not respond to indomethacin.

On initial ophthalmic examination, his best corrected visual acuity was 20/400 in the right eye and 20/20 in the left eye. Intraocular pressures were normal. The left eye was normal. Slit-lamp biomicroscopy of the right eye revealed normal findings except for cells in the anterior vitreous. Funduscopic examination of the right eye demonstrated a yellow submacular choroidal lesion with overlying intraretinal and subretinal haemorrhage (Fig 1). Localised retinal thickening and subretinal fluid were noted. There were no cells in the posterior vitreous.

Ultrasonography of the right eye showed an acoustically hollow choroidal mass with low internal reflectivity measuring 3·0 mm in depth. Overlying subretinal fluid and superficial choroidal infiltration were noted. The lesion blocked choroidal background fluorescence in the venous phase of fluorescein angiography (Fig 2). Mottled areas of increased fluorescence developed within the lesion as the study progressed and there was diffuse staining of the surrounding retinal vessels. Progressive leakage from the lesion, and persistent blockage owing to the retinal haemorrhage were evident during the recirculation phase (Fig 3).

A transvitreal fine-needle aspiration biopsy was performed by a previously described technique to obtain diagnostic material from the lesion.[2] A bent 25 gauge needle was inserted through pars plana at 8 o'clock and passed in a transvitreal fashion into the lesion under indirect ophthalmoscopic guidance. The needle was connected via plastic tubing to a 10 ml syringe and a small amount of diagnostic material was aspirated into the needle bore. Aspiration was then stopped and the needle gently removed from the eye. Minimal haemorrhage at the biopsy site was curtailed with tamponade and

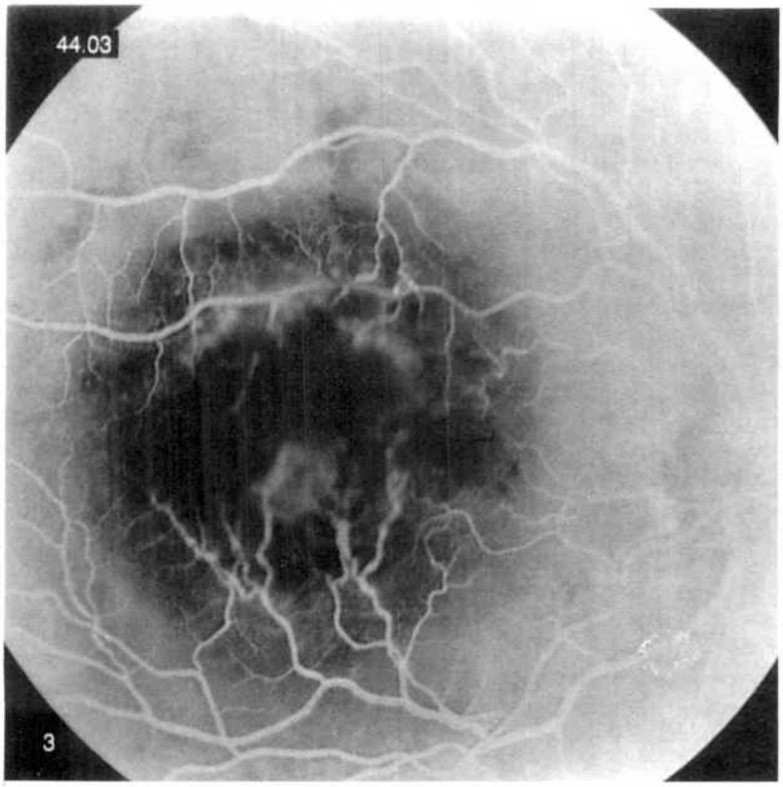
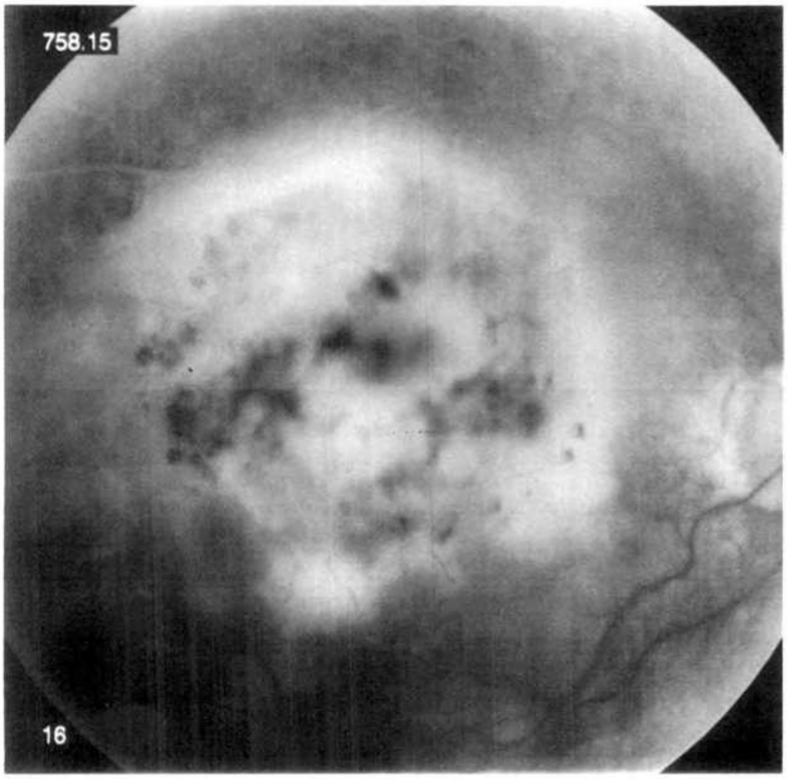


Figure 2 Fluorescein angiogram of the right eye (venous phase) showing blockage of choroidal background fluorescence by the lesion.

balanced salt solution was injected to raise the intraocular pressure to normal. The needle was then removed from the connector tube and immediately immersed in saline solution. The saline was aspirated through the needle, flushing the material into the syringe. All material obtained was then submitted for microbial and cytological examination which showed acute and chronic inflammatory cells and red blood cells. No organisms or leukaemic cells were seen. The Gram stain showed Gram positive, branching, filamentous organisms consistent with *Nocardia*. *Nocardia asteroides* was isolated in a microbiological culture. The organism was sensitive to amikacin, cefotaxime, erythromycin, trimethoprim, and sulphamethoxazole. No other organisms were identified.

Figure 3 Fluorescein angiogram of the right eye (recirculation phase) showing progressive leakage from the lesion.



Therapy with parenteral trimethoprim/sulphamethoxazole was instituted and the patient was evaluated for systemic nocardiosis. Computed tomography (CT) revealed approximately 35 small presumed nocardial abscesses in the brain. It should be noted that at this time the patient was not experiencing any symptoms that were believed to be related to CNS nocardiosis. Additionally, synovial fluid aspirated from the patient's painful right shoulder demonstrated organisms compatible with *Nocardia asteroides*. The systemic nocardiosis responded somewhat during a 1 month period of intensive intravenous treatment. A repeat CT scan of the brain approximately 4 months later demonstrated resolution of the CNS lesions, and the right shoulder pain had abated. The choroidal abscess appeared to enlarge somewhat over the following 4 months and the patient was subsequently given intravitreal injections of amikacin (400 μg) and cephazolin (Ancef, USA) (2·25 mg). Over the next 3 months, the abscess became an elevated, subretinal fibrotic mass with a resultant visual acuity of hand movement in the right eye. Visual acuity in the left eye remained 20/20, with a normal ocular examination. Currently, the patient is maintained on oral co-trimoxazole and the visual acuity is unchanged.

Discussion

Historically, nocardial infections in humans are very rare and often self-limited. Their frequency and severity are increasing, however, as immunosuppressive and chemotherapeutic agents are used more frequently.[3] The use of cyclophosphamide and steroids in combination has been shown experimentally to increase susceptibility to nocardial infection.[3]

Nocardia asteroides, a member of the order Actinomycetales, is a slow growing, Gram positive, variably acid-fast, filamentous aerobic organism that inhabits the soil.[4] The organism grows readily over a wide temperature range and on relatively simple media. *Nocardia asteroides* and *Nocardia brasiliensis* are the two most common species that cause morbidity in humans with *N asteroides* accounting for about 90% of the cases. The infection is commonly acquired via the pulmonary route by inhalation of the organism, or subcutaneously by direct contamination of an open skin wound. The pulmonary lesions tend to simulate tuberculosis or histoplasmosis. Approximately 50% of patients with pulmonary nocardiosis have haematogenous dissemination, particularly to the brain.[5] Currently, trimethoprim-sulphamethoxazole is the drug of choice for treating nocardiosis. In cases of antibiotic resistance or allergy, either amikacin, minocycline, or ampicillin and erythromycin in combination have been found to be effective. *Nocardia* also shows susceptibility to some of the second and third generation cephalosporins. Although our patient's CNS and arthropic infection appeared to respond to treatment, the ocular lesion demonstrated progression. Antibiotic resistance is unlikely since the brain abscesses and right shoulder pain resolved during treatment. It is possible that although both trimethoprim and sulphamethoxazole serum levels were in the therapeutic range, these levels may be insufficient to eradicate an intraocular infection. To our knowledge therapeutic levels of trimethoprim and sulphamethoxazole have not been determined for intraocular nocardial infections, nor have serum levels been correlated with aqueous or vitreal levels.

In the case presented, a patient with known CLL on immunosuppressive therapy developed decreased vision in his right eye. Ophthalmic examination disclosed a submacular choroidal abscess. Previously, the patient had been hospitalised for numerous pulmonary infections and more recently developed right shoulder pain. Though not proved, it is probable that *Nocardia* was a causative agent in some of these pulmonary infections. We speculate that haematogenous dissemination from the lungs resulted in nocardial infection in the eye, shoulder, and CNS.

In immunocompromised patients with chorioretinal infiltrative lesions, opportunistic organisms are frequently the causative agents. In this, and a previously described case,[5] transvitreal fine-needle aspiration biopsy of the lesion led to early, accurate identification of the organism. Appropriate antibiotic therapy and systemic work-up were then implemented early in the course of the infection. This is particularly important as a delay in appropriate therapy is associated with increased morbidity and mortality.

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Eye movement tics

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Abstract

An 8-year-old girl presented with opsoclonus-like eye movement and an 18 month history of intermittent facial tics. Investigations were all normal. Electro-oculography showed the eye movements to be of variable amplitude (10–40 degrees), with no intersaccadic interval, and with a frequency of 3–4 Hz. Saccades, smooth pursuit, optokinetic, and vestibular reflexes were all normal. These abnormal eye movements eventually disappeared. It is thought that they were a form of ocular tics.
(*Br J Ophthalmol* 1992; **76**: 697–699)

Tics are quick, involuntary, and repetitive muscular movements that can be transient or persistent, local or widely generalised.[1] It is common for children with tics to present to a paediatrician with accompanying symptoms of emotional disturbances. Tics are common in childhood with a prevalence of 13% and an age of onset of 6–12 years.[2] By the age of 7 years, approximately 5% of children have a history of such abnormal movement disorders.[3] Most often tics originate with facial movements which then may gradually extend to other parts of the body. They may be a continuum from mild, simple, suppressible tics to chronic multiple, and complex ones.[4-6] Most childhood tics resolve spontaneously and, in patients with multifocal tics, the last to resolve are often eye blinking tics.[7]

The few eye movement tics reported in the literature have been associated with ocular and facial tics and resembled nystagmus.[8] Frankel and Cummings[9] reported eye rolling tics in a group of patients with Tourette's syndrome who also had blepharospasm. Binyon and Prendergast[10] presented three cases with ocular tics: one had infantile autism and Tourette's syndrome, another had other types of tics that were complicated by neurological, behavioural, and educational problems. Their third patient had isolated eye movement tics that eventually disappeared. Opsoclonus-like eye movements have not been reported.

Case report

An 8-year-old girl was referred because of episodes of bizarre eye movements. She was born to unrelated parents following a normal pregnancy by forceps delivery. There were no neonatal problems and her development was normal. She was a very bright, intelligent, outgoing child and well above average academically. She was the older of two children. There was a family history of a grandfather who had multifocal tics as a child but this did not include eye movements.

At the age of 6·5 years she developed symmetrical facial tics which became more frequent and florid over the next 4 months. These continued on and off for 12 months, though they did subside substantially. No neurological or physical abnormalities were found. Eighteen months after the initial onset of tics she developed episodes of lid retraction, convergence, and rotatory nystagmus of which she appeared to be unaware. The duration of these episodes was 5–15 seconds and they varied from a couple of episodes a day to repeated attacks lasting for much of the day. Initial investigations of computed tomographic scan of the brain, electroencephalogram, ultrasound of the adrenals, and 24 hour catecholamine excretion were all normal. These tests were performed because the original provisional diagnosis was that of dancing eye syndrome.

On admission to hospital neurological examination was found to be normal, with full external ocular movements. When questioned about her eye movements she said that she 'sometimes knows it is going to happen', though she often appeared to be unaware of them. She was also capable of initiating and suppressing these oscillations.

Urine creatinine and homovanillic acid levels were normal. Magnetic resonance imaging, repeat electroencephalogram, brainstem and visual evoked potentials, and electroretinograms were also normal. Electro-oculographic eye movement studies were carried out and a video recording was taken of the opsoclonus. Five weeks after her hospital admission the anomalous eye movements had completely resolved.

EYE MOVEMENT RECORDINGS

Horizontal eye movements were recorded using electro-oculography (EOG) and they were monitored on video. The chaotic saccadic bursts occurred without any intersaccadic intervals, and in the horizontal and vertical planes, thus fulfulling the criteria of 'opsoclonus'.[11]

Our patient exhibited bursts of conjugate, rotatory, and pendular oscillations. The ampli-

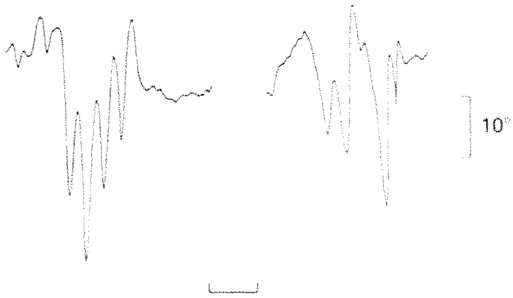

Figure 1 Horizontal electro-oculogram depicting the opsoclonus. Two typical examples of the spontaneous eye oscillations.

tude of the horizontal components was rather variable and ranged from 10 to 40 degrees with a frequency of 3–4 Hz (Fig 1). These eye movements were often observed in association with eyebrow raising, facial grimacing, and, on some occasions, with arm and leg extensions and slight arching of the back.

Saccades were normal. Smooth pursuit gain was 1·0 at 20 deg/s. Full field, binocular optokinetic nystagmus gain was 0·9 at 25 deg/s. Vestibular nystagmus in the dark had a peak gain of 0·9, with a chair acceleration of 18 deg/s/s up to 80 deg/s. The vestibular time constant was estimated to be 15 seconds. These results are all within the normal limits for our laboratory. However, short episodes of opsoclonus were evident throughout the testing session and the oscillations were superimposed upon the normal eye movements.

Discussion

Opsoclonus is a rare but striking disorder of ocular motility. It is characterised by involuntary, chaotic bursts of multidirectional, high amplitude, high frequency saccades, without an intersaccadic interval.[11] The absence of intersaccadic intervals distinguishes opsoclonus from macrosaccadic oscillations.[12]

In children opsoclonus usually occurs in one of three settings: transient neonatal opsoclonus,[13] parainfectious or encephalopathic opsoclonus, and the syndrome of opsoclonus and myoclonus,[14] which can be neuroblastoma related. This has also been known as 'dancing eye syndrome', 'myoclonic encephalopathy', and 'infantile polymyoclonia'[15]; and is characterised by an acute or subacute onset of polymyoclonia, cerebellar ataxia, and opsoclonus.

Precise localisation of the lesion causing opsoclonus remains uncertain,[16,17] and studies have shown mild to severe loss of cerebellar Purkinje cells.[18–21] It is likely that with the complex neuronal network involved in the generation of saccades, there may be more than one anatomical site involved in the pathogenesis of opsoclonus.[22]

In our patient a diagnosis of 'dancing eye syndrome' was rejected owing to the lack of other clinical symptoms and to the characteristics of the oscillations. They were of lower frequency (3–4 Hz) than in opsoclonus recorded from patients with brainstem and cerebellar pathology, including children with 'dancing eye syndrome', which are in the order of 10 Hz.[23] Studies[11,24] have reported a wide frequency range for opsoclonus (from 5 to 13 Hz) yet our patient's saccadic frequency remains outside this range. Another unusual feature of the opsoclonus in our case was the large variability in the amplitude of the oscillations.

Simultaneous video and EOG recording enabled careful and continuous monitoring of the patient's behaviour. Our patient did have some accompanying facial motor behaviour, the most common being eyebrow raising, retraction, and twitching of the eyelids during the bout of opsoclonus and facial grimacing just prior to its onset. Opsoclonus has been reported together with eyelid movement and twitching,[25] blinking,[16] and lid retraction.[26] However these signs usually present together with other manifestations such as ataxia, myoclonus, and tremor. Thus, the possibility of ocular tics was entertained.

Tics possess three features that can help differentiate them from other movement disorders[27]: (1) they are often preceded by a sensation and an irresistible urge to move[28]; (2) they can be wilfully suppressed; and (3) they persist in all stages of sleep.[29] We did not record our patient's eye movements during sleep but they were consistent with the first two features.

It has been thought that tics are manifestations of underlying psychological conflict. Our patient's ocular tics could be considered as a form of 'conversion disorder'. This is defined as a disturbance of physical functioning that cannot be explained by pathophysiological mechanisms but is due to psychological conflict or need.[30] Studies suggest that conversion symptoms usually develop in children with pre-existing vulnerabilities: they tend to have academic problems, be conscientious, perfectionistic, and egocentric.[31] Our patient was noted to be very intelligent, hyperactive, and outgoing though IQ was not formally assessed. Studies also suggest that those with tics have above average intelligence,[32,33] but they perform better only on tests involving psychomotor speed and reaction times[4]; this has been interpreted to represent an exaggerated motor response to stress.

The association of stress and anxiety with tics has been well documented.[4,6,34] Through discussions with the patient's parents it became apparent that they had high expectations of their daughter and it was revealed that the onset of her symptoms occurred soon after the birth of the second child. This could well have been the 'stressor' to initiate and exacerbate her symptoms, to which she may have already had a predisposition.

The possibility was raised that the eye movements may be voluntary. Voluntary nystagmus and flutter occur in normal subjects and can also be learnt.[35] They are usually associated with a convergence effort, but this was not observed in our case.

Though the abnormal eye movements have disappeared it is important to follow up this patient in case of any further symptoms. We believe this is a form of ocular tics. Follow-up studies[4] have shown that two thirds of patients recover completely, with the best prognosis being for children whose onset of tics was between 6 and 8 years of age.

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Primary uveal B immunoblastic lymphoma in a patient with AIDS

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Abstract

A case of primary intraocular malignant lymphoma without cerebral involvement is reported in a 30-year-old man with acquired immunodeficiency syndrome. The study of the enucleation specimen showed a B immunoblastic lymphoma with a CD30 positive anaplastic large cell component. There was no involvement of the adenexal structures of the orbit. The patient subsequently completed non-surgical staging showing no extension of the tumour. The clinical course was rapidly fatal with dissemination to the pericardium and pleura.

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Among extranodal localisations of malignant lymphomas arising in acquired immunodeficiency syndrome (AIDS) patients, the eye is very rarely affected as a primary site. Most cases involve primitive cerebral or systemic malignant lymphomas, initially associated with an orbital localisation or secondary extension to the orbit.[1 2] We describe the first localisation of a primitive and strictly intraocular lymphoma in an AIDS patient.

Case history

The patient, a 30-year-old Caucasian man, was an intravenous drug abuser and known to be seropositive for the human immunodeficiency virus (HIV) since April 1988. Treatment with azidothymidine was initiated in January 1989. One year later a tuberculosis was diagnosed by the study of an axillary lymph node. In April 1990 uveitis of the right eye developed followed by painful blindness. A computed tomography scan of the orbit showed an enhancing mass in the posterior and anterior chambers of the eye, displacing the lens posteriorly and invading the cornea (Fig 1). A haemorrhagic effusion was observed in the vitreous chamber. Enucleation was performed. Microscopic examination showed the intraocular tumour to be an immunoblastic malignant lymphoma. Computed tomographies of the brain, thorax, and abdomen were negative. Bone marrow aspirate and biopsy were normal. Cerebrospinal fluid examination revealed no cells suggestive of lymphoma. The chest *x* ray showed a fluid effusion in the pleura and pericardium. Numerous malignant immunoblasts were found in both effusion fluids. In spite of an evacuating puncture the patient died of acute respiratory distress. Autopsy was not permitted.

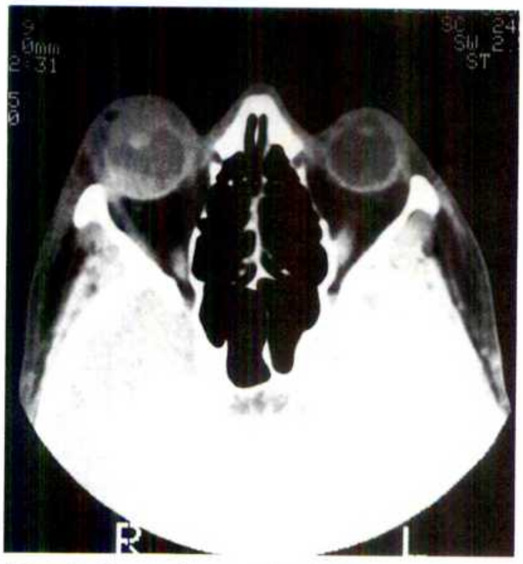

Figure 1 Computed tomography of orbit. Intraocular mass involving the anterior segment. Haemorrhagic effusion in the vitreous chamber.

Methods

The eye was fixed in Bouin's solution, embedded in paraffin, and stained with haematoxylin and eosin, Gordon Sweet's silver impregnation, and periodic acid Schiff. For immunohistochemical study, paraffin sections were analysed, using the ABC peroxidase method (Vectastain ABC Kit) with the following monoclonal antibodies: CD45, CD45 RO (UCHL 1), CD30 (Ber H2), anti-EMA, CD20 (L26), L26 (Dakopatts), CD15 (Immunotech), CD43 (MT1), MB2 (Biolyon), anti-A, G, M, immunoglobulin heavy chains, and kappa, lambda, light chains (Becton Dickinson).

Results

The eye measured 3 cm (anteroposterior diameter) by 2·7 cm (transverse diameter). The anterior segment was deformed and occupied by a white, crumbly, and poorly limited mass measuring 1 cm, destroying the iris and displacing the lens posteriorly. A haemorrhagic effusion was present in the vitreous chamber. On histological study the tumour appeared to consist of a proliferation of large lymphomatous cells. Giemsa staining showed these cells to have a large basophilic cytoplasm and round pale nucleus with one or two large central nucleoli (Fig 2). Some had an eccentric nucleus. A number of the large cells had a moderately basophilic cytoplasm with an irregular nucleus, and were sometimes binucleated (Fig 2). Small lymphocytes with irregular nuclei and thick chromatin were admixed with the large lymphomatous cells. The tumour infiltrated the anterior

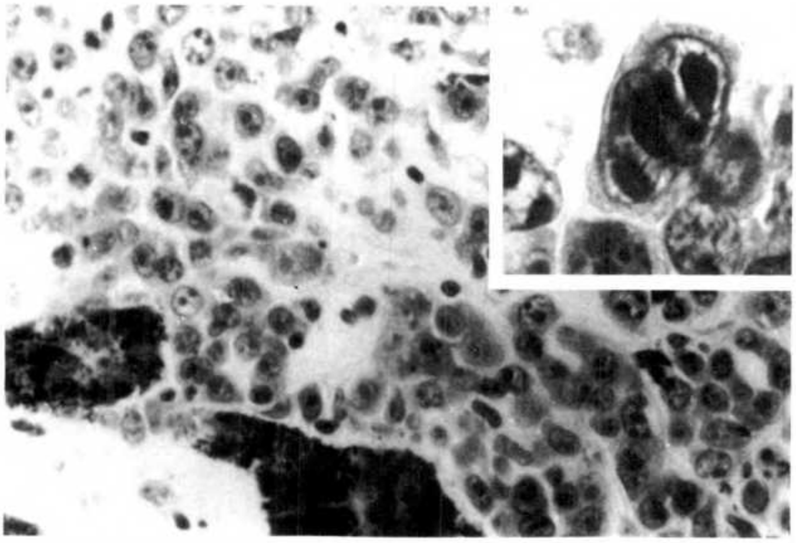

Figure 2 High grade lymphoma of the immunoblastic type (Giemsa stain, ×280). Sheets of lymphomatous cells infiltrating the ciliary processes and showing plasmocytic differentiation. Inset: anaplastic large cells with irregular nuclei and prominent nucleoli (haematoxylin and eosin, ×1575).

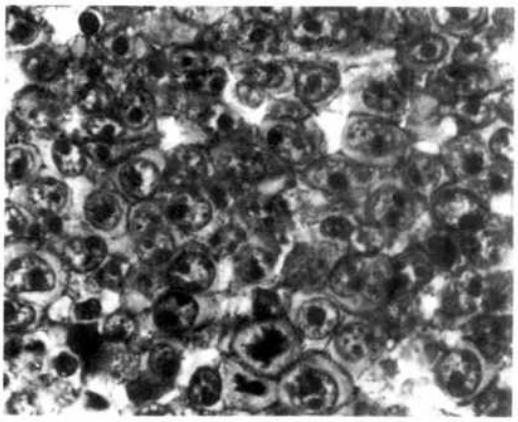

Figure 3 Immunoblastic lymphoma. The neoplastic cells expressed CD45 antigen (ABC peroxidase stain, ×560).

and posterior chambers, the cornea, the ciliary muscle, and processes. Large necrotic areas were seen in the tumour infiltrate. The immunohistochemical study showed that all the tumour cells strongly expressed CD45 on the cell membrane (Fig 3). Ninety percent of the tumour cells showed intracytoplasmic staining and juxtanuclear reinforcement with the MB2 antibody. Thirty percent of the tumour cell population corresponding to the large cells with irregular nuclei were positive for the anti-CD30 antibody. All the tumour cells expressed the EMA. Small lymphocytes with thick chromatin were marked with the anti-CD45 RO antibody corresponding to reactive T-lymphocytes. The study with anti-CD15 antibody, anti-CD20 (L26), and the antibodies against heavy and light immunoglobulin chains was negative. The morphological and immunohistochemical appearance of this tumour led us to diagnose high grade B malignant lymphoma of the immunoblastic type, with plasmocytic differentiation associated with a small CD30 positive anaplastic large cell population.

Discussion

Among extranodal localisations of malignant lymphomas in AIDS, ocular tumours are exceptional and have not been reported at all in many series involving numerous patients.[3-7] Only a few cases of orbital lymphomas in AIDS patients have been reported in the literature.[1 2 8-11] The first case of orbital lymphoma in AIDS, a Burkitt's lymphoma, was published by Fujikawa *et al* in 1983.[8] In 1984, Brooks *et al* described another case of Burkitt's lymphoma arising in the orbit without any intraocular involvement.[1] The initial evaluation of extension showed systemic diffusion with localisations in the bone marrow and testicles but without diffusion to the central nervous system. In a series of 88 extranodal lymphomas occurring in HIV positive homosexual men, Ziegler *et al* noted two localisations in the orbit.[9] In 1986, Di Carlo *et al* reported a non-documented case of lymphoma of the orbit in an autopsy study of 30 AIDS patients who died of malignant lymphoma.[10] In another study, extranodal involvement by non-Hodgkin's lymphoma was identified in 77 patients and one case of conjunctiva lymphoma was cited.[11] In an autopsy series of 25 AIDS patients, Jabs *et al* also reported an ocular localisation of a malignant lymphoma.[12] De Girolami *et al* noted one case of large cell B lymphoma arising in the eye with cerebral localisation.[2] The histological type of some of these lymphomas was not described.

In our case the initial localisation was intraocular, restricted to the uveal tract. The evaluation of extension did not demonstrate any systemic or cerebral localisation. The discovery of numerous immunoblastic cells with plasmocytic differentiation in the pleura and pericardial effusion accounted for secondary systemic dissemination.

In non-AIDS patients intraocular lymphomas are rarely localised in the uveal tract and most often involve the vitreous chamber, the retina, and the optic nerve.[13 14] In a review of 28 cases of intraocular lymphomas involving an HIV seronegative population, lymphomas of the uveal tract could invade the brain. But most frequently they showed systemic dissemination without involvement of the central nervous system.[13] In Trudeau's series, comprising 87 cases, initial and isolated ocular localisation represented 60% of cases.[14] In more than 80% of these cases the evolution of the disease consisted of multivisceral dissemination.

As in other localisations of lymphomas in AIDS, our case is a high grade malignant lymphoma with B phenotype. Moreover, a group of anaplastic large cells expressing CD30 antigen and EMA was associated with the immunoblastic proliferation cells. Such anaplastic large cell component has been described in association with large cell lymphomas of both B or T-cell type.[15]

In summary, malignant lymphomas initially arising in the eye are exceptional in AIDS patients. In all the cases reported in the literature localisation in the eye is associated with a systemic dissemination or a simultaneous or secondary localisation.[1 2] We report the first primitive and initially strictly intraocular lymphoma in AIDS.

As in Brooks' observation this ocular localisation can resemble an ocular infection, for example persistent uveitis or choroidis,[1 14] which is frequently seen in AIDS.[12] In our case the initial diagnosis was tuberculous uveitis in a patient already treated for lymph node tuberculosis. Primitive intraocular lymphoma should therefore always be suspected in AIDS patients with symptoms of chronic uveitis or choroiditis, since the early recognition of this disorder is essential for appropriate treatment.

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LETTERS TO THE EDITOR

Research into quinine ocular toxicity

EDITOR,—Quinine ocular toxicity presents a major clinical problem in which, after the initial amaurosis, central vision recovers at least partially after a number of days in most cases, but a characteristic constriction of the peripheral fields remains permanently.[1] The mechanisms are disputed but may include an early toxic effect on retinal ganglion cells and a late toxic effect on retinal arteries.[1-3] Methods of reversal are unsatisfactory: for example, stellate ganglion blockade may be dangerous and is of doubtful efficacy.[4,5] Retrobulbar injection of vasodilator drugs is also unproved.

Recently we have advised the use of intravenous nitrates in cases presenting to the National Poisons Information Service and preliminary experience suggests that it may be beneficial. We here report two examples. Case 1 was a 16-month-old child who, following accidental ingestion of quinine sulphate tablets, had a quinine plasma concentration of 32·5 mg/l. Intravenous nitrates were used in treatment. Amaurosis was detected on admission but had resolved completely on review 6 weeks later. Case 2 (male 36 years), an attempted suicide, presented with total blindness, 8–10 hours after ingestion. A plasma quinine concentration of 5·28 mg/l was found on admission. Intravenous nitrates were commenced and there was evidence of recovery within 1–2 hours, which was eventually total. We would be pleased to hear of further cases, and we can advise on the regimen on a 24 hour basis.

This treatment is safe and non-invasive and its effectiveness may be secondary to a preferential increase in the retinal vascular bed flow which supplies the ganglion cells as opposed to the choroidal bed which supplies the remainder of the retinal layers.

We are also setting up research into the mechanisms of quinine toxicity and would be pleased to see acute cases in the Department of Ophthalmology, St Thomas's Hospital for scanning laser ophthalmoscopy within 36 hours of overdose. Patients can be reassured that the investigation is non-invasive.

D MOORE
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Guy's Hospital, and
St Thomas's Hospital Medical School,
London

1 *Grant's toxicology of the eye*, 3rd ed. Springfield, IL: Thomas, 1986.
2 Buchanan TA, Lyness RW, Collins AD, Gardiner TA, Archer DB. An experimental study of quinine blindness. *Eye* 1987; 1: 522–4.
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5 Boland ME, Brennand-Roper SM, Henry JA. Complications of quinine poisoning. *Lancet* 1985; i: 384–5.

Eye injuries in children caused by aerosols and sprays

EDITOR,—In compiling a district profile of childhood accidents, we investigated eye injuries to children attending the emergency outpatient clinic of the ophthalmology department at Darlington Memorial Hospital. Eye injuries caused by aerosols and other sprays were identified as a potential area for prevention.

The ophthalmology emergency outpatient register for 1990 was analysed for children aged 16 years and under who presented with a new episode of eye injury. The clinical records of those suffering injuries caused by sprays were reviewed to determine type of spray and outcome. During the year 1990 there were 90 new attendances owing to accidental eye injuries in children reported at Darlington Memorial Hospital. Of these, five (6%) were explicitly caused by sprays (Table I). Three children were discharged from the clinic without follow up following emergency assessment and appropriate treatment. One child with superficial punctate keratitis and one with corneal erosion were discharged following a review in clinic after 1 and 5 days respectively. The estimated cost of treating these patients for the seven outpatient assessments was £266.

Table 1 Age, sex, type of spray, and clinical findings of children presenting with aerosol or spray related eye injuries at the emergency ophthalmology outpatient clinic during 1990

Age	*Sex*	*Type of spray/aerosol*	*Clinical findings*
2	M	Polish	Dermatitic reaction
3	M	Perfume	Superficial keratitis
14	M	Perfume	Corneal erosion
16	M	Fire extinguisher	Red eye
16	F	Deodorant spray	None recorded

A computerised literature search using Medline has revealed no epidemiological literature on the subject and only one reference (non UK) which related to an ocular injury in children caused by an artificial snow spray.[1] Furthermore, the Childhood Accident Prevention Trust library knew of no reference to aerosol or spray injuries to children's eyes (personal correspondence). This perceived lack of interest may be because of a high level of under reporting of such injuries.

The Department of Trade and Industry, National Home Accident Surveillance System (HASS) database for 1989 revealed only eight cases of childhood eye injuries as a result of sprays or aerosols. Types of spray included car paint, polish, silicone waterproofing, and toilet aerosol. If an annual figure of five new cases in one district general hospital ophthalmology outpatient clinic holds nationally, the level of under reporting is profound and the cost to the NHS is high.

In conclusion we would like to say that childhood eye accidents caused by aerosols or sprays are a potentially preventable cause of morbidity to children. Many of the injuries may be mild but could be potentially very serious. Their epidemiology is unresearched. At present they may be seriously under reported, giving rise to a lack of awareness of the problem. Certainly the above highlights a gap in the literature which requires filling through further research.

EDWIN J PUGH
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PHILIP MACKIE
Darlington Health District

1 Ben-Nissan D, Savir H. Ocular injury by artificial snow spray. *Harefuah* 1990; 119: 370.

BOOK REVIEWS

Colour Atlas/Text of Ophthalmic Parasitology. By B H Kean, Tsieh Sun, Robert M Ellsworth. Pp 234. US$ 110·00. Igaku-Shoin: New York, 1991.

This colour atlas and text on eye diseases caused by parasites fills a gap in the ophthalmic literature. The text is complemented by colour and black-and-white photographs. Pictures include clinical appearances, gross pathology, and photomicrographs.

Over 30 parasites are described, classified as protozoa, nematodes, cestodes, trematodes, and arthropods. Chapters have sections on epidemiology, parasitology, clinical features of the systemic diseases, ocular manifestations, pathology, laboratory diagnosis, and treatment. Each chapter concludes with a list of references and appropriate illustrations.

The lead author (B H Kean) originally determined to write this book 30 years ago. Together with his coauthors a most welcome text has been published. Well illustrated, well referenced, the text draws together the complexities of parasitology with what have been 'obscure' clinical ophthalmic findings for the vast majority of ophthalmologists.

It is a relief to have such a book at hand, for reference in the western world where ocular disease may not present in recognised form and for obvious practical application in the developing countries of the world where a low-cost edition could become required reading.

D D MURRAY McGAVIN

Manual of Systematic Corneal Surgery. By Arthur D McG Steele, Colin M Kirkness. Pp 104. £40. Churchill Livingstone: Edinburgh, 1992.

In times when even small subjects are covered in large multi-authored texts a small effective book on a large subject is a welcome change. It is aimed 'as an aid to corneal surgery for the surgeon who does not regularly perform this type of work, whether he' (and presumably she) 'is a junior doctor in training or an established practitioner.' The two authors are well known for their experience in corneal surgery and their strongly held views; both of these attributes are put to good use in the book. It is at its best when describing the stepwise procedures to the surgeon reader who has already decided to undertake a particular operation. The authors describe how to do the procedures which have worked well for them. They do this without oblique discussion and without hint of uncertainty and only the occasional need to consider alternatives. The surgical methods are clearly described and the illustrations are appropriate and helpful. The clarity of the text and the conviction with which issues are presented have resulted in a commendable, tree-sparing size with fewer than 90 pages of text. Despite the brevity, the aims of the authors have been achieved admirably. The book is an ideal resource for surgeons who need to carry out surgical procedures on the cornea, and therefore should be of interest to the majority of ophthalmologists.

DOUG COSTER

Electrodiagnostic Testing of the Visual System: A Clinical Guide. By Ronald E Carr and Irwin M Siegel. Pp 188. £33.61. F A Davis: Philadelphia, 1990.

This short textbook is very readable and contains the fruits of many years of experience in the clinical application of electrophysiological techniques. Those who have read the authors' previous textbook will find that this is a completely rewritten and new book and it includes much new information. There is, for example, a useful section on the pattern ERG. Unfortunately any textbook in this field is likely to omit some of the latest research developments – for example, scotopic threshold responses, but the commonsense approach in the book will be very refreshing for anyone contemplating the maze of literature already available. The book is primarily concerned with visual electrophysiological techniques from the point of view of the clinical ophthalmologist but I would recommend it to anyone with an interest in 'bioelectrics'.

N R GALLOWAY

Laser: Its Clinical Uses in Eye Diseases. 2nd edn. By Ian J Constable and Arthur Siew Ming Lim. Pp 208. £65.00. Churchill Livingstone: Edinburgh, 1990.

This is the second edition of an already, and deservedly, popular book by two authors of international repute. It has been deliberately kept small, concentrating on current lasers and the treatment of ocular disorders routinely seen. It is aimed at updating the busy ophthalmic clinician, is easy to read, and is liberally illustrated with numerous excellent clinical photographs, angiograms, and diagrams.

It is divided into two sections, the larger being Laser Photocoagulation of the Posterior Segment and the smaller Anterior Segment Laser Applications. In the first section there are chapters covering the principles, techniques, limitations, complications, management, and treatment of conditions including diabetic retinopathy, other vasculopathies, central serous retinopathy, age-related macular degeneration and subretinal neovascularisation, tears, detachments, and tumours. In the second section there are chapters on the principles of YAG laser photodisruption, laser modalities in glaucoma, posterior capsule photodisruption, miscellaneous laser applications, safety, and some practical exercises.

The excellence of this book includes the photographs and illustrations, the chapters on complications, the photocoagulation management and treatment of diabetic retinopathy, disciform tears and detachment, and argon laser iridotomy. Some chapters could have been better and in particular it would have been useful to have had an expanded section on YAG laser iridotomy. There are numerous minor inaccuracies, some out-dated practices and photographs and some of the text is scientifically woolly. In some chapters the references could have been more up to date.

Laser technology is changing apace and there is only little mention of the excimer and diode lasers. There is now a plethora of newer therapeutic contact lenses and there is no mention of fundal examination non-contact lenses, such as the 90 dioptre.

Despite these faults it is a useful book and I would have no hesitation in adding it to our library.

J JAGGER

MCQs in Ophthalmology. By Anthony Vivian and Ruth Manners. Pp 190. £12.95. Butterworth-Heinemann: Oxford, 1992.

This book is a useful addition to the growing numbers of MCQ texts available for the postgraduate student in ophthalmology. The sections are clearly delineated and where explanations of the answers are deemed necessary, the authors present these in a clear and authoritative manner, though stating in the prefix that the reader might find some of the answers controversial or ambiguous.

This is a well prepared and useful aid for both the postgraduate student and teacher preparing for higher examinations.

J WILLIAMSON

Books received

Year Book of Ophthalmology 1991. By Peter R Laibson. Pp 292. £42. Wolfe Publishing: London, 1991.

Lens Surfacing Handbook. By Clifford W Brooks. Pp 138. £18.95. Butterworth-Heinemann: London, 1992.

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (Mastercard, Visa, or American Express), stating card number, expiry date, and full name.

NOTES

How safe are the medicines you take?

A one day conference entitled 'How safe are the medicines you take?' will be held on 19 November 1992 at the Royal York Hotel, Station Road, York, YO2 2AA, UK. For further details: Conference Department, The Royal Society of Health, 38A St George's Drive, London SW1V 4BH. (Tel: 071-630 0121; Fax: 071-976 6847.)

Extended Programs in Medical Education

The Department of Ophthalmology, University of California School of Medicine, San Francisco, offers a course entitled 'Ophthalmic Surgical Complications: Oops – What Do I Do Now?' to be held 10–12 December 1992 at the Ritz-Carlton Hotel and UCSF Campus, San Francisco. Further details: School of Medicine, Room LS-105, Extended Programs in Medical Education, University of California, San Francisco, CA 94143–0742, USA. (Tel: (415) 476–4251.)

Biomedical Optics '93

An international symposium sponsored by the Biomedical Optics Society will be held on 16–22 January 1993 at the Los Angeles Airport Hilton Hotel, Los Angeles, California, USA. *Maiman Award:* The Laser Centers of America and the Biomedical Optics Society have established the Theodore Maiman Award to help authors of outstanding papers submitted to the symposium from countries where currency is not easily convertible. There will be up to 10 awards, each of $2000. For further details: Biomedical Optics Society, PO Box 10, Bellingham, Washington 98227–0010, USA. (Tel: (206) 676–3290; Fax: (206) 647–1445.)

1993 Update in the Management of Age-Related Macular Degeneration – Optimal Fluorescein Angiography Workshop

This workshop will be held on 22–23 January 1993 at The Wilmer Ophthalmological Institute of the Johns Hopkins Medical Institutions, Thomas B Turner Building, Johns Hopkins Medical Institutions, Baltimore, MD, USA. Further details: Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Education, Turner 20, 720 Rutland Avenue, Baltimore, MD 21205, USA. (Tel: (410) 955–2959; Fax: (410) 955–0807.)

XIV Congress of Asia-Pacific Academy of Ophthalmology

The XIV Congress of Asia-Pacific Academy of Ophthalmology will be held on 24 to 28 January 1993 at the Hotel Sonargaon, Dhaka, Bangladesh. For details please contact: APAO Secretariat, OSB Bhaban, PO Box No 8021, Mirpur, Dhaka-1216, Bangladesh. (Fax: 880–2–804522.)

American Academy of Ophthalmology

The American Academy of Ophthalmology has released a clinical education videotape on phacoemulsification entitled 'Making the Transition to Phacoemulsification.' It is designed for extracapsular cataract extraction surgeons wishing to learn the technique. Price $65 for academy members and $85 for nonmembers. Further details: American Academy of Ophthalmology, 655 Beach Street, San Francisco, CA 94109–1336, USA. (Tel: (415) 561–8500; Fax: (415) 561–8567.)

Ro-Man-Aid

The Romanian Multiple Sclerosis Association is pleading for specialist equipment, especially diagnostic eye equipment, as they have none! Their list of priorities includes; biomicroscope, sets of lenses for prescriptions, ophthalmoscope, tonometer, sets of Snellen charts, books and sets of plates for testing for colour blindness (Isihara, Velhagen, Rapkin, etc). If you have any suitable surplus equipment contact: Rosa Drown, Secretary, Ro-Man-Aid, 12 Bayr Grianagh, Castletown, Isle of Man. (Tel: 0624 823065.)

vcm

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BRITISH JOURNAL OF
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Editorial

Local anaesthesia for eye surgery

The trend towards local anaesthesia in preference to general anaesthesia in eye surgery increases apace for several reasons, not least of which is the move towards day case surgery. In many countries, local anaesthesia is the norm not only for cataract, glaucoma, and lid surgery but for squint surgery and for more prolonged procedures such as vitreoretinal surgery. The question which exercises the minds of surgeons is which is the simplest, most effective, and safest procedure for local anaesthesia. Currently there are several techniques including retrobulbar, peribulbar, sub-Tenon's, and subconjunctival,[1] and some surgeons perform cataract surgery only with topical anaesthesia.[2,3]

The increasing use of peribulbar anaesthesia can be partly attributed to its reputation for a reduced risk of complications including retrobulbar haemorrhage, globe perforation, optic nerve injury, and respiratory arrest from brain stem anaesthesia. Peribulbar anaesthesia is used with good effect in most forms of ocular surgery including retinal detachment surgery.[4] However, peroperative complications are not eliminated by peribulbar anaesthesia, especially globe perforation in which axial length has been identified as the greatest single risk factor.[5]

'Each to his own' one might say, since all of these procedures appear to work well in experienced hands. Most surgeons, however, continue to use the technique they know best and there is little doubt that retrobulbar anaesthesia is still commonly practised. Many surgeons have also been taught to believe that Atkinson's position, wherein the globe is positioned in an upwards and inwards position, is the preferred position to achieve optimal anaesthesia.[6] However, previous studies suggested that this was more likely to cause injury to the optic nerve, and to increase the relative risk of brain stem anaesthesia and respiratory arrest.[7] This study suffered from the drawback that it was performed on cadavers and might not have been applicable to the in vivo situation.

In this month's issue of the journal, Liu *et al* report on the intraorbital anatomical relations of the optic nerve in vivo using the sensitive 'STIR' magnetic resonance imaging technique and confirm that in Atkinson's position the optic nerve would adopt a sinuous course which lies dangerously close to the path of the needle during administration of a retrobulbar anaesthetic. They recommend that the globe be positioned in a downwards and inwards position and, in addition, the skin of the lower lid be gently pinched at the site of injection with the effect of elevating the globe out of the path of the needle. These recommendations should be considered by any surgeon who practises retrobulbar anaesthesia particularly with modern disposable, long and sharp needles. Atkinson's original paper recommended the use of short (2·5–3·5 cm) blunt needles which may not traverse the orbit sufficiently to enter the nerve sheath, but the risk is probably not worth taking.

J V FORRESTER

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British Journal of Ophthalmology 1992; 76: 706–710

ORIGINAL ARTICLES

Seasonal variations in the onset of retinal vein occlusion

Sohan Singh Hayreh, M Bridget Zimmerman, Patricia Podhajsky

Abstract

Seasonal variation in the development of retinal vein occlusion in 1003 consecutive patients with various types of retinal vein occlusion was studied prospectively from 1973 to 1990. No seasonal variation in the onset of any type or combination of types of retinal vein occlusion was found. This refutes previous reports of such seasonal variation, which were based on small retrospective series.

(*Br J Ophthalmol* 1992; 76: 706–710)

Seasonal variation in the incidence of development of central retinal vein occlusion[1] and 'retinal vein occlusion'[2] has been reported during the past 5 years. Lavin and Dhillon,[1] in a retrospective study of 105 central retinal vein occlusion (RVO) cases, found a significantly ($p<0·001$) higher incidence during the 6 month period from September to February than for the 6 month period from March to August. They stated that variation in onset of central RVO was very similar to the variations in seasonal temperature. The seasonal variation in their study was similar for both ischaemic and non-ischaemic central RVO. Peduzzi *et al*[2] reported from a retrospective study of 127 Italian patients (from Modena, Italy) with 'retinal vein occlusion' that the incidence of RVO was significantly higher ($p<0·005$) during the cold months (42·5%) than during the warm (26·7%) and intermediate (30·7%) months, with no significant difference between two latter groups.

In the literature, there are also reports of higher incidence of myocardial infarction, cerebrovascular accidents, transient ischaemic attacks, and thrombosis during the winter than other seasons, attributed to the colder temperature.[3-8]

In view of these reports, we investigated seasonal variation in the development of various clinical and pathogenetic types of RVO. The study is based on our consecutive 1003 patients with various types of RVO, where the pertinent information was available, and who were studied prospectively from 1973 to 1990. Our study showed no seasonal variation in the onset of any type of RVO individually or collectively.

Materials and methods

The source of information is a prospective, comprehensive study of patients with various types of RVO, who have been seen in the ocular vascular clinic of the University Hospitals and Clinics at Iowa City since 1973. We analysed the data of 1003 patients with various types of RVO, seen consecutively in the clinic from 1973 until the end of 1990.

CLASSIFICATION OF RETINAL VEIN OCCLUSION

To obtain scientifically valid information, it is essential to classify RVO into its different types. Our long-term studies on RVO have shown that in fact there are the following six distinct groups, each one of them with very different pathogenesis, clinical presentation, course, and management:

(A) *Central retinal vein occlusion.* Our experimental and clinical studies have demonstrated that this must be divided into the following two distinct entities[9 10]: (i) non-ischaemic type (or venous stasis retinopathy); (ii) ischaemic type (or haemorrhagic retinopathy).

(B) *Hemi-central retinal vein occlusion.* This variant of central RVO was discovered by us,[11] and, like central RVO, this type has two distinct subtypes: (i) non-ischaemic hemi-central RVO (or hemi-venous stasis retinopathy); (ii) ischaemic hemi-central RVO (or hemi-haemorrhagic retinopathy).

(C) *Branch retinal vein occlusion.* This requires to be further subdivided into two types: (i) major branch RVO involves one of the four major retinal branch veins; (ii) macular branch RVO involves one of the venous tributaries in the macular region.

Pathogenetically, central RVO and hemi-central RVO are identical in nature except that, in the former, the one trunk of the central retinal vein is occluded, while in the latter there are two anomalous trunks, only one of which is occluded in the optic nerve. Thus for purposes of data analysis, to determine characteristics in different permutations and combinations of RVO, we have grouped our patients into the following 13 categories:

I *Central retinal vein occlusion group,* comprising;
(1) All cases of this group combined.
(2) Non-ischaemic type only.
(3) Ischaemic type only.
II *Hemi-central retinal vein occlusion group* comprising:
(4) All cases combined.

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22 July 1992

Table 1 Number of patients and episodes of retinal vein occlusion in its 13 categories defined in the text

Type of retinal vein occlusion	*Category*	*Number of patients**	*Number of episodes†*
Central retinal vein occlusion:			
Total cases	1	557	653
Non-ischaemic type	2	439	467
Ischaemic type	3	179	186
Hemi-central retinal vein occlusion:			
Total cases	4	129	138
Non-ischaemic type	5	96	97
Ischaemic type	6	38	41
Central retinal vein occlusion + hemi-central retinal vein occlusion:			
Total cases	7	675	791
Non-ischaemic type	8	531	564
Ischaemic type	9	216	227
Branch retinal vein occlusion:			
Total cases	10	345	373
Major branch retinal vein occlusion	11	250	268
Macular branch retinal vein occlusion	12	102	105
Total cases of retinal vein occlusion	13	1003	1164

*The total number of patients in the last line does not add up to the total for the six types of retinal vein occlusion (ie categories 2, 3, 5, 6, 11,12) because some patients had more than one type of retinal vein occlusion. Similarly in categories 1, 4, 7, and 10 the total patients do not add up to their respective two subtypes because some patients had more than one subtype of retinal vein occlusion.

†Second episode of the same type of retinal vein occlusion in the same eye was excluded in this analysis.

(5) Non-ischaemic only.

(6) Ischaemic only.

III *Central and hemi-central retinal vein occlusions combined group* (ie I + II above) because of their pathogenetic similarity:

(7) All cases combined.

(8) Non-ischaemic only (ie 2+5 above).

(9) Ischaemic only (ie 3+6 above).

IV *Branch retinal vein occlusion group* comprised:

(10) All cases in this group combined.

(11) Major branch RVO only.

(12) Macular branch RVO only.

V (13) *All types of retinal vein occlusion combined* (ie 2+3+5+6+11+12 above).

As mentioned above, since central RVO and hemi-central RVO are pathogenetically similar in nature, in the data analyses we have also combined the two categories, to explore the subject further. In this data analysis, each episode of development of RVO is counted as an independent event. For example, an eye might have had major branch RVO and later on might have macular branch RVO – that would mean two episodes of RVO in that eye. Similarly, an eye may first develop non-ischaemic central RVO and that may later on change to ischaemic central RVO: that would be counted as two episodes of RVO in that eye. Several eyes developed a second episode of the same type of RVO, but that was not included in the analysis of episodes in this study. Table 1 gives details of number of patients and episodes of RVO in the 13 categories list above. The total number of patients in the last line in Table 1 does not add up to the total number of patients for the various types of RVO because several patients had more than one type of episode of RVO simultaneously or successively, in the same or in the fellow eye. Similarly, in Table 1, the total patients (that is, in categories 1, 4, 7 and 10) do not add up to their two respective subtypes because some patients had more than one subtype.

INCLUSION CRITERIA FOR THE STUDY

(1) We included in this study only those patients where a definite diagnosis of one of the six types of RVO could be made, based on the various inclusion criteria listed below.

(2) Since the time of onset of RVO is an important consideration in this study, every effort was made to establish this information as accurately as possible. It was almost invariably based on the history given by the patient. In some patients, however, retinal examination revealed a disparity between the history and examination – that is, the fundus findings indicated the RVO to be older than the history; such patients were excluded from the study. In a few non-symptomatic patients, duration of disease at first examination was assessed from the fundus findings, based on our experience of natural history of RVO in a large series over the past 25 years.

(3) All patients with inadequate information or doubtful diagnosis were excluded.

DIAGNOSTIC CRITERIA FOR VARIOUS TYPES OF RETINAL VEIN OCCLUSION

(A) *Central retinal vein occlusion.* This was classified as non-ischaemic or ischaemic, based on the combined information obtained from visual acuity, visual fields (done with a Goldmann

Table 2 Seasonal variation: result of goodness-of-fit tests

		Month		*Quarter*		*Season*		*Temperature*	
Type of retinal vein occlusion	*Sample size**	χ^2 *(df=11)*	*p value*	χ^2 *(df=3)*	*p value*	χ^2 *(df=3)*	*p value*	χ^2 *(df=2)*	*p value*
Central retinal vein occlusion:									
All patients	653	11·280	0·4201	3·752	0·2895	1·393	0·7071	0·626	0·7313
(a) Non-ischaemic type	467	7·570	0·7512	4·424	0·2191	1·252	0·7405	0·086	0·9577
(b) Ischaemic type	186	18·955	0·0619	0·586	0·8995	0·654	0·8840	2·923	0·2319
Hemi-central retinal vein occlusion:									
All patients	138	10·276	0·5057	4·406	0·2208	3·170	0·3662	2·783	0·2487
(a) Non-ischaemic type	97	9·180	0·6053	4·284	0·2324	2·441	0·4860	1·378	0·5020
(b) Ischaemic type	41	7·838	0·7278	1·847	0·6048	2·194	0·5330	1·973	0·3728
Central retinal vein occlusion + hemi central retinal vein occlusion:									
All patients	791	11·116	0·4336	5·067	0·1670	2·366	0·5001	0·975	0·6143
(a) Non-ischaemic type	564	7·720	0·7382	5·822	0·1206	1·887	0·5961	0·051	0·9750
(b) Ischaemic type	227	15·266	0·1706	1·232	0·7454	0·623	0·8911	2·529	0·2824
Branch retinal vein occlusion:									
All patients	373	12·401	0·3343	3·290	0·3490	1·876	0·5986	3·357	0·1866
(a) Major type	268	12·774	0·3083	2·342	0·5044	2·552	0·4660	1·571	0·4558
(b) Macular type	105	17·439	0·0955	5·828	0·1203	0·854	0·8365	2·363	0·3069
All types of retinal vein occlusion:	1164	11·702	0·3865	5·768	0·1235	3·733	0·2918	3·125	0·2096

*Number of episodes of retinal vein occlusion.

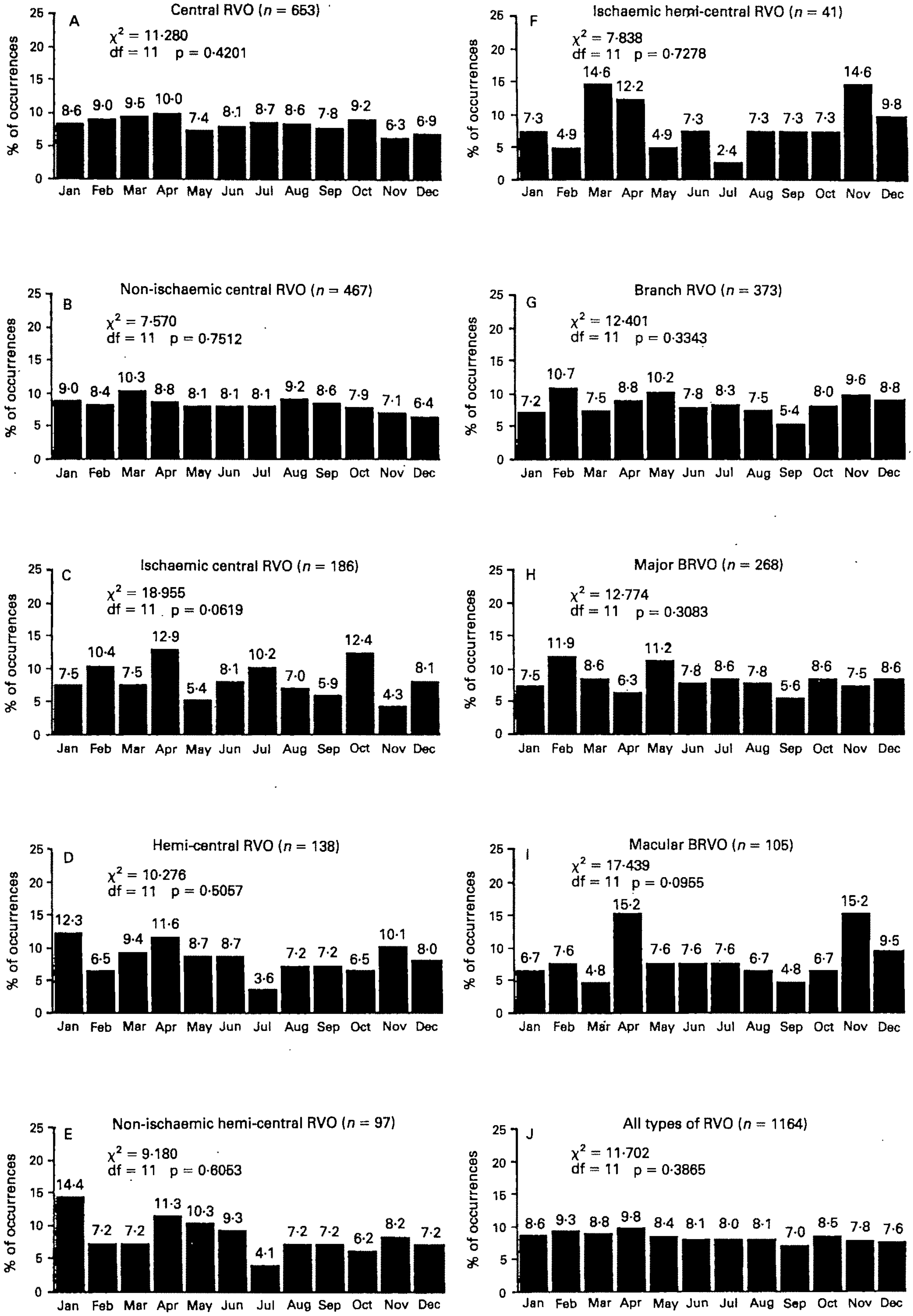

Figure 1 The distribution of occurrences of onset of retinal vein occlusion (RVO) of various types (A to J, see Table 1) by calendar months with χ^2 of goodness-of-fit test statistic and corresponding p value.

perimeter), relative afferent pupillary defect, electroretinopathy, ophthalmoscopy and fluorescein fundus angiography, as discussed elsewhere.[9 10] We made every attempt to exclude other retinopathies mimicking central RVO.

(B) *Hemi-central retinal vein occlusion.* We have described criteria to define non-ischaemic and ischaemic varieties of this type of RVO elsewhere.[11]

(C) *Branch retinal vein occlusion.* In eyes with 'major branch retinal vein occlusion' one of the four major branch retinal veins had to be occluded near, or rarely at the optic disc. In eyes with 'macular branch retinal vein occlusion' the macular venule had to be occluded.

In some cases, follow-up information provided a definite diagnosis if it was doubtful at the initial visit.

DATA ANALYSIS

For each category of RVO the null hypothesis tested was:

Ho: there is no seasonal variation in onset time, against the alternative hypothesis:

Ha: there is seasonal variation in onset time.

Seasonal variation in the onset of various types of RVO were examined in four different ways.

(1) By *calendar month.*
(2) By *quarters of the year:*
  (a) January to March
  (b) April to June
  (c) July to September
  (d) October to December.
(3) By *seasons of the year:*
  (a) *Winter:* December to February
  (b) *Spring:* March to May
  (c) *Summer:* June to August
  (d) *Fall:* September to November
(4) By *temperature of the season* in this part of the country:
  (a) *Cold:* November to March (average: High −1 to +8°C and low −1 to −11°C).
  (b) *Mild:* April, May, October (average: high 16 to 22°C and low 4 to 11°C).
  (c) *Hot:* June to September (average: high 24 to 30°C and low 13 to 18°C).

Each of the four time divisions was examined in the 13 categories of RVO described above. Each disease category and time group was first analysed without considering age or gender. Subsequent analyses tested for association between seasonal groups and age and sex. The statistical test used to test the hypothesis of no seasonal variation was the χ^2 goodness-of-fit test. If there is no seasonal variation in onset of disease then we would expect an equal rate of occurrence. The goodness-of-fit test[12] determines if there are significant statistical departures from expected values. A p value of 0·05 was used to determine significant differences. In performing these statistical tests, when both eyes were involved, each occurrence in each eye was considered as an independent event. Occurrence of any of the six types of RVO in the same patient in the same eye was also considered as an independent event. When a patient had multiple episodes of the same type of RVO in the same eye, only the first episode was included in the analysis.

Analysis of the data using log-linear model was also done. The log-linear model included sex, age at onset, and time of onset (using the categories defined above for seasonal variation) as the factors in the model. The patients were divided into three age groups, in accordance with the criteria used by the US National Center for Health Statistics, US Public Health Services[13]: *young* (less than 45 years old), *middle-aged* (45 to 64 years old), and *elderly* (65 or older). Interaction of *time* of onset with *sex* and *age* were examined to determine if *sex* of patient and/or *age* at onset should be considered when testing for seasonal variation in onset tme.

Results

The log-linear model analysis showed that *time* of onset showed no significant association with *sex* and *age* at onset. Thus, seasonal variation was tested over males and females and all age groups combined.

Table 2 summarises the results of the χ^2 goodness-of-fit test. Figure 1 shows the distribution of occurrences of onset of RVO of various types (A to J) by calendar months with the χ^2 goodness-of-fit test statistic and corresponding p value. For each of the different types of RVO, the test results show no significant departure from the assumed model of equal rate of occurrence of RVO. The other analyses, by quarters of the year, by seasons of the year, and by temperature, showed similar results (Table 2). The p values obtained from the χ^2 goodness-of-fit tests ranged from $p=0{\cdot}1203$ to $p=0{\cdot}9750$ (Table 2).

Discussion

Our study does not bear out the finding of seasonal variation in the development of RVO reported in two previous studies.[1 2] One study was from London and based on retrospective review of information of 105 cases of central RVO.[1] The other report was from Modena, Italy and based on a retrospective study of 127 patients with 'retinal vein occlusion'[2] – the authors give no information about the number of various types of RVO included in their study. Lavin and Dhillon[1] argued that a seasonal incidence of central RVO may be comparable with thrombotic lesions in other organs, because myocardial infarctions and cerebrovascular accidents are more frequent in winter than other seasons and show close correlations with temperature,[3-8] and that cold temperature is associated with an increased risk of thrombosis.[5]

It could conceivably be argued that differences in living conditions in Britain and Italy on the one hand, and the midwestern United States on the other, could be responsible for our not finding any seasonal variation. Such a hypothesis is, however, hard to maintain. The winter temperatures in Iowa are much lower (average: high −1 to +8°C and low −1 to −11°C), for much longer, than in London (England) (average: high 7 to 11°C and low 2 to 8°C) or Modena (Italy) (average: high 9 to 14°C and low

2 to 8°C). Buildings and cars which are well-heated during winter are almost universal in Iowa compared with the other two countries, so that the indoor temperature in Iowa is likely to be much warmer than in Britain and Italy during winter. It might be just possible to claim that this difference is responsible for our not seeing any seasonal variation. This possibility has also been suggested by a study indicating that the lowest seasonal variation occurs in countries with very cold winters (for example, Scandinavia) which would imply that insulation and indoor heating may be preventive factors.[14] However, it is hard to find much support for this argument. A British study found that elderly people living in centrally heated warden-controlled accommodation showed similar seasonal variation in mortality rates to those living in their own (non-centrally heated) homes.[15] Also, one of us (SSH) can attest from years of residence in Britain and Iowa that the British and other Europeans dress much more warmly at home than Iowans do, so that the effect of central heating in Iowa is counterbalanced by the warmer clothes in Europe. Moreover, the hypothetical beneficial effects of central heating in Iowa would be counteracted by the extreme cold often experienced when a person goes outdoors during winter, whether of necessity or for recreation, as was also pointed out by Keatinge.[15] Further, Keatinge *et al*[16] in their study in England and Wales found that with an increase in proportion of households with central heating from 13% to 69% from 1964 to 1984, there was no significant decrease in excess winter mortality from coronary and cerebrovascular disease. The study by Stout and Crawford[8] from Belfast, Northern Ireland, suggested that central heating may not greatly increase minimum indoor temperature or influence core body temperature at all. The centrally heated accommodation in Iowa therefore cannot explain the marked disparity between our results and those of the other two studies.

A more likely explanation of the disparity of results betwen ours and the two European studies lies in their relatively small samples and the retrospective nature of their data collection. It is generally well-accepted that information retrieved retrospectively from old records, gathered from routine visits to a busy clinic, cannot be relied upon to produce scientifically valid results. Our study, on the other hand, was a well planned, prospective study whose data can be confidently relied upon.

CONCLUSIONS

Our prospective study on a large sample of different types of RVO showed no seasonal variation in their development.

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Acyclovir ointment plus topical betamethasone or placebo in first episode disciform keratitis

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Abstract

Thirty patients with first episode disciform keratitis and with no previous steroid exposure were randomly assigned to double blind treatment with 3% acyclovir ointment and 0·1% betamethasone (Betnesol) drops or acyclovir ointment and matching placebo. In the steroid group 14 of the 15 patients healed in a mean time of 21·8 days. In the placebo group eight of the 13 patients healed in a mean time of 34·5 days. The difference in mean healing time between the two groups was significant ($p<0{\cdot}05$). The cumulative rate of healing was also quicker in the steroid group when compared with the placebo group ($p<0{\cdot}001$). Other clinical parameters improved more favourably in the combination treatment group. Four patients, two in either group, experienced a mild transient punctate epitheliopathy, but no other serious adverse effects were noted. There has been no significant difference in the recurrence rate between the two groups after a mean follow-up period of approximately 3 years.

(*Br J Ophthalmol* 1992; **76**: 711–713)

Acyclovir ophthalmic ointment (3%) used five times daily has been shown to be effective in the treatment of dendritic and geographic keratitis.[1,2] Therapy with acyclovir has been associated with a low incidence of mild transient adverse effects, namely stinging and punctate epitheliopathy.[3]

The aetiology of disciform keratitis is unclear but has been postulated to be viral in origin with an associated delayed type hypersensitivity reaction to herpes antigen within the stroma or endothelium.[4-6] A combination of antiviral and steroid would seem to be the optimal therapeutic choice. Acyclovir is a good candidate as it is able to penetrate the intact corneal epithelium and stroma, achieving therapeutic levels in the aqueous humour.[7] In a previous study we have shown that a combination of acyclovir and dilute steroid was significantly more effective than acyclovir alone in healing herpetic disciform keratitis.[8] However in that study a significant number of patients had been previously treated with corticosteroids which may have affected the results. The aim of this current study was to compare the efficacy of 3% acyclovir ophthalmic ointment and 0·1% betamethasone drops (Betnesol) with 3% acyclovir ointment and placebo for the treatment of first episode disciform keratitis in patients who had no history of previous steroid treatment.

Table 1 Patient demography

Parameter	*Acyclovir + placebo (SD)**	*Acyclovir + betamethasone (SD)**
Age	45 (25)	53·8 (24)
Corneal thickness	1·06 (0·18)	1·05 (0·18)
Uveitis:		
flare	1·53 (0·51)	1·73 (0·81)
cells	1·13 (0·52)	1·4 (0·83)
Duration of symptoms (days)	11·7 (8·0)	10·7 (9·5)
Symptoms (0–3)		
pain	1·20 (0·86)	1·33 (1·0)
photophobia	2·0 (0·98)	2·33 (0·72)
lacrimation	1·87 (0·91)	2·0 (0·93)
grittiness	1·20 (0·94)	1·33 (0·98)

*Values given are mean with standard deviation (SD)
All values not significant

Materials and methods

Thirty patients with a clinical diagnosis of disciform keratitis were included in the study. Informed consent to participate in the study was obtained from all patients or parents of children, where appropriate. Uniocular patients, patients who had previous ocular surgery, or patients who had received steroid treatment at any time prior to the study were excluded. Diagnosis was based on the history and clinical appearance of the cornea. Details of a history of previous cutaneous herpes or a documented history of previous ocular herpetic ulceration obtained from the patients' notes were recorded. Patients were seen as often as clinically necessary and at all visits a full ocular examination was carried out.

At presentation the area of involved cornea was measured and was scored as follows; 1=0–25%, 2=25–50%, 3=50–75%, 4=75–100%. The presence of neovascularisation, either superficial or deep and in how many quadrants, was also recorded. Symptoms of pain, photophobia, lacrimation, and grittiness were scored at each visit on a four point scale (0=absent, 1=mild, 2=moderate, 3=severe). The following parameters were also assessed at each visit; visual acuity, conjunctival injection, epithelial oedema, stromal oedema, folds in Descemet's membrane, endothelial deposits, anterior chamber flare and cells, intraocular pressure, and corneal thickness using a Haag-Streit pachometer. A record was also made of any adverse effects potentially attributable to the treatment.

Patients were randomly assigned to treatment with 3% acyclovir ophthalmic ointment and either 0·1% betamethasone drops or placebo in a double blind manner. Treatment was applied to the affected eye five times daily. The eye was not padded. If patients showed deterioration over 5 days or if the condition remained static for 14 days, they were withdrawn from the study. The keratitis was regarded as healed when the corneal thickness had returned to normal, when epithelial and stromal oedema had regressed, when endothelial deposits had either disappeared or were old in appearance, and when there was no more activity in the anterior chamber. Patients continued on drops and ointment for 14 days after healing was complete. Over the next 5 weeks the treatment was tapered by reducing the frequency of daily dosage by one each week.

The *t* test was used to compare treatment groups for age, initial corneal thickness, duration of symptoms, severity of uveitis. The Wilcoxon signed rank test was used to compare initial scores for pain, grittiness, lacrimation, photophobia, and severity of uveitis.

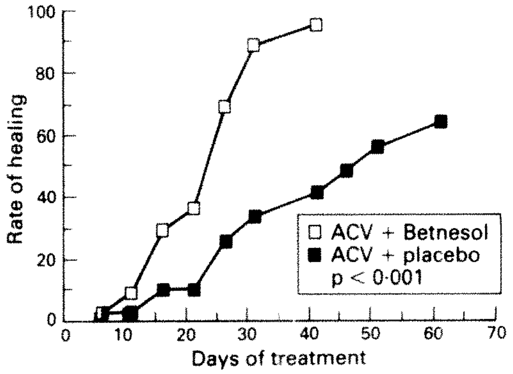

Figure 1 Cumulative healing rate of treatment modalities.

Results

Fifteen patients were treated with acyclovir and betamethasone and 15 received acyclovir and placebo. The mean age in the steroid group was 53·8 years with a range of 11 to 92 years. The mean age in the placebo group was 45 years with a range of 7 to 77 years. There were 12 males and three females in the steroid group and 11 males and four females in the placebo group. Twenty eight of the 30 patients (14 in each group), had either a history of previous cutaneous herpes or a previously documented dendritic ulcer. One patient in either group did not give a clear history of a previous herpetic infection but the appearance in both was that of a typical herpetic disciform keratitis. A comparison of pretreatment parameters showed no significant differences between the two groups at the 10% level (two-tailed test). These results are presented in Table 1.

Two patients in either group had superficial corneal neovascularisation limited to one quadrant at presentation. None of the other 28 had evidence of corneal neovascularisation at presentation. The extent of corneal involvement at presentation between the two groups is shown in Table 2. There was no significant difference between the two groups.

Two patients in the placebo group were lost to follow up. Of the remaining 13 patients in this group eight healed in a mean time of 34·5 days, where five were withdrawn from the study. Fourteen of the patients in the steroid group healed in a mean time of 21·8 days and one patient was withdrawn. A comparison of the mean healing time between the two groups showed that the patients in the steroid group healed in a significantly faster time than those in the placebo group ($p<0·05$). There was also a significantly greater number of withdrawals in the placebo group in comparison with the steroid group, five out of 13 versus one from 15 ($p=0·035$, Fisher's exact test). One patient in the steroid group was withdrawn as he developed progressive deep corneal neovascularisation encroaching on the visual axis. He was subsequently admitted to hospital for treatment and healed in 10 days on acyclovir five times daily and betamethasone four times daily. Five patients in the steroid group were withdrawn; three because of worsening uveitis and two because of the development of progressive deep corneal neovascularisation. The five patients were subsequently treated with acyclovir and dilute steroid. All healed in a mean time of 17 days on this treatment.

Table 2 Percentage area of corneal involvement at presentation

	0–25%	*25–50%*	*50–75%*	*75–100%*
Acyclovir+placebo (15 patients)	5	7	3	0
Acyclovir+steroid (15 patients)	4	6	4	1

The cumulative rate of healing was also examined in both groups and compared using the Mantel Cox test (Fig 1). Patients receiving acyclovir and steroids healed at a significantly faster rate ($p<0·001$).

Uveitis and corneal thickness tend to be responsive to steroid treatment. The improvement in these clinical parameters at the end of the study was particularly noticeable in the acyclovir and betamethasone group. From the results presented in Table 3 it can be seen that the patients in the steroid group responded more favourably and virtually all showed improvement. However five patients in the placebo group showed no improvement.

Symptoms of pain, photophobia, lacrimation, and grittiness completely resolved in 14 of the 15 patients receiving acyclovir and betamethasone. In contrast only seven of 13 acyclovir and placebo treated patients had a similar response. However it must be remembered that a large number of this group were withdrawn from the study with active keratitis.

Of the 14 patients who healed in the steroid group, there were seven recurrences (four dendritic ulcers and three cases of disciform keratitis) after a mean follow-up time of 34·5 months. There were three recurrences (two dendritic ulcers and one case of disciform keratitis) in the eight patients who completed the trial in the placebo group after a mean follow-up

Table 3 Progression of corneal thickness and uveitis

		Acyclovir+ placebo (n=13)	*Acyclovir+ betamethasone (n=15)*
Corneal thickness			
same		5	0
better		8	15
worse		0	0
Uveitis			
same	(flare)	3	1
	(cells)	2	1
better	(flare)	10	14
	(cells)	11	14
worse	(flare)	0	0
	(cells)	0	0

of 33·4 months. This difference was not significant (p=0·68).

The only adverse event recorded was a mild transient punctate epitheliopathy seen in four patients, two in either group.

Discussion

The aetiology of disciform keratitis is not fully understood. It is not certain whether it is caused by viral replication within keratocytes and subsequent cell lysis or whether viral antigen entering the corneal stroma alters keratocyte antigenicity and subsequently results in a delayed type hypersensitivity reaction to the herpes antigen within the stroma or endothelium.[9] This uncertainty in aetiology is reflected in the differing views on treatment of this condition.

McGill, using topical acyclovir alone in patients who had not previously had topical steroids, reported a good response in 14 of 15 such patients in an open label non-placebo controlled trial.[10] The mean healing time was 44·3 days. However in the present study only eight out of 13 such patients healed on topical acyclovir alone whereas 14 of 15 healed in a shorter time of 21·8 days on the combination therapy. We also found no significant difference in the recurrence rate between the two groups after a follow-up period of nearly 3 years. This is particularly interesting as there have been fears expressed that the use of steroids in the treatment of first episode disciform keratitis may lead to a higher recurrence rate.[10]

In this study acyclovir combined with 0·1% betamethasone produced a more rapid response with significantly fewer treatment failures than acyclovir and placebo. We therefore conclude that acyclovir without steroids does not provide effective control of first episode disciform keratitis in patients who had not had previous steroid therapy.

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Topical ofloxacin compared with gentamicin in the treatment of external ocular infection

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Abstract

In a double-masked, randomised, controlled study the effectiveness and safety of 0·3% ofloxacin solution were compared with those of 0·3% gentamicin ophthalmic solution in treating external bacterial ocular infections. The clinical improvement rate for patients treated with ofloxacin was 98% (51/52) and 92% (48/52) for those treated with gentamicin. Microbiological improvement was achieved in 78% (40/51) of the ofloxacin patients, compared with 67% (35/52) of the gentamicin group. Ofloxacin treatment eradicated or controlled 85% (86/101) of the Gram positive and 89% (17/19) of the Gram negative organisms cultured, compared with 83% (103/124) and 78% (29/37), respectively, after gentamicin treatment. None of these differences were statistically significant. The incidence of adverse effects attributable to ofloxacin treatment (3·2%) was less than that reported for gentamicin (7·1%). Ofloxacin proved to be an effective, safe, and comfortable therapy for external bacterial ocular infection.

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The aminoglycosides gentamicin and tobramycin are well established as first-line therapy for external ocular infections, and possess a broad spectrum of activity against Gram positive and Gram negative organisms.[1-3] However, resistance to these antibiotics is increasing. For example, resistance to topical aminoglycoside therapy may be encountered in as many as 8% to 10% of ulcerative keratitis cases caused by *Pseudomonas aeruginosa*.[4] Resistance appears to be even greater in ocular infections caused by Gram positive organisms.[5] Adverse drug effects such as punctate epithelial keratitis are encountered in some patients.[3] The problems of resistance to the aminoglycosides and the possibility of adverse responses to these agents in some patients have given impetus to the search for new ocular anti-infective agents.

Ofloxacin is among the more promising agents under investigation as a treatment for ocular infections.[6] An in vitro study demonstrated that ofloxacin is more potent than non-quinolone antibiotics (gentamicin, tobramycin, chloramphenicol, polymyxin B) and more potent than the quinolone, norfloxacin, against various ocular species, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus pneumoniae*.[7] In another recent in vitro study comprising five fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, and temafloxacin) with gentamicin, tobramycin, and cefazolin, the fluoroquinolones had excellent in vitro activity against isolates of common bacterial pathogens, and were less toxic to the corneal epithelium than the aminoglycosides.[8] Ofloxacin also shows potent activity in vitro against chlamydial species, various anaerobes, and other species.[9-24]

Fluoroquinolones, such as ofloxacin, derive their antibacterial activity from their ability to inhibit bacterial DNA gyrase, an enzyme that catalyses the conversion of relaxed covalently closed circular DNA to a supercoiled form.[25] These compounds alter the structure and disrupt the function of bacterial DNA and interfere with fundamental processes, including DNA replication, recombination, repair, and transcription. Ofloxacin-resistant bacterial strains do not form readily in vitro, and when such strains do appear they generally are not as viable as ofloxacin-sensitive strains.[26 27] Cross resistance with ofloxacin and other classes of antibiotics has not been reported.

In clinical studies conducted to date, topical ofloxacin has significantly reduced the clinical signs and symptoms of ocular infection and eradicated the causative organism in a high proportion of patients.[28] The present study was designed to assess the clinical value of topical ofloxacin treatment by comparing its efficacy, safety, and comfort of application with those of standard topical gentamicin therapy.

Subjects and methods

PATIENTS

A total of 194 patients with suspected external ocular bacterial infection, including conjunctivitis, blepharitis, and blepharoconjunctivitis,

Table 1 Exclusion criteria

Patients were excluded from the study if any of the following were present:

(1) Active ophthalmic disease (except external bacterial infection)
(2) Uncontrolled systemic disease, such as hypertension or diabetes
(3) Use of other topical ophthalmic medications
(4) Use of concomitant systemic antibiotics
(5) Sensitivity to test medications or solution components
(6) Pregnancy or nursing, or planned pregnancy during the study

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were enrolled at 18 study sites. All patients signed informed consent forms describing the design and purpose of the study as well as the potential risks of participation. None of the patients were known to be sensitive to the test medications or solution constituents, such as benzalkonium chloride, or to nalidixic acid, gentamicin, or any other aminoglycoside. These and other exclusion criteria are shown in Table 1.

DRUG TREATMENT

Patients were randomly assigned to receive either 0·3% ofloxacin (n=93) or 0·3% gentamicin (n=98), administered in identical masked bottles. One drop of either ofloxacin or gentamicin solution was applied to the affected eye(s) six times daily (every 2 to 4 hours) for 2 days (day 1 and day 2) and then four times daily for the next 8 days (day 3 to day 10). The first dose was administered by the investigator, and all subsequent doses were self-administered by the patient. Patients were instructed to discontinue use of the study medication at least 12 hours prior to the second follow-up examination on day 11.

PATIENT EXAMINATION, CULTURE EVALUATION

During a baseline examination, medical and ophthalmic histories were taken, visual acuity tested, biomicroscopy and ophthalmoscopy performed, symptoms of ocular infection assessed, and conjunctival and eyelid specimens obtained. Sensitivity testing of the clinical isolates for ofloxacin, gentamicin, and tobramycin was performed with the Kirby Bauer disc diffusion method. The patients were re-examined on days 3 to 5 and again on day 11. The follow-up examinations on day 11 consisted of the same clinical observations as the baseline examinations and also included the investigator's evaluation of the effectiveness of the treatment and an assessment of the comfort of the drug treatment. In patients with positive baseline culture findings, follow-up culture tests were performed at the day 11 examination.

At all follow-up examinations, the safety of the drug treatments was evaluated by noting adverse reactions and changes from baseline in visual acuity, ophthalmoscopic findings, and lens pathology. Comfort of the test medications was evaluated based on the severity of burning, stinging, tearing, itching, foreign body sensation, photophobia, blurring of vision, dryness, and pain experienced after applying the study medication.

To obtain ocular cultures, standard calcium alginate swabs were moistened with sterile unpreserved saline and rolled along the lid margins and conjunctival cul-de-sacs of each affected eye. Separate lid and conjunctival cultures were taken for each eye. Each culture swab was placed in a sterile tube with 1·0 ml of transport-dissolving buffer, and was delivered to the microbiological laboratory within 4 hours of collection.

For quantitative analysis in the laboratory, the tube was vortexed until the swab fibres were finely dispersed. A sample of the suspension was plated directly on to a 5% horse blood agar plate and a chocolate agar plate. A dilution (1:10) of the sample was prepared in sterile trypticase soy broth and was also plated onto both blood and chocolate agar plates. Colony-forming units were counted after all plates were incubated for 48 hours at 37°C in 4% CO_2. Bacteria were identified and sensitivity tests (Kirby Bauer disc diffusion method) to ofloxacin, tobramycin, and gentamicin were performed.

DATA ANALYSIS

Drug efficacy assessment was restricted to patients with positive baseline culture results, based on the criteria of Cagle *et al*[3] (Table 2). Baseline culture findings were positive in 52 of 93 subjects (56%) treated with ofloxacin and in 53 of 98 (54%) subjects in the gentamicin group.

The microbiological improvement rate – that is, the proportion of patients evaluable for efficacy who had improved microbiologically, was determined by evaluating the change from baseline in bacterial colony counts. Microbiological outcomes, based on the worst outcome of all species at all culture sites, were classified as follows: *proliferated* (bacterial colony count positive, based on species-specific criteria listed above and greater than baseline); *no change* (bacterial colony count equal to baseline); *reduced* (bacterial colony count less than baseline but still greater than the species-specific threshold listed above); *controlled* (bacterial colony count less than the species specific threshold listed above); or *eradicated* (bacterial colony count equals zero). Patients were considered to have improved microbiologically if

Table 2 Drug efficacy assessment[a]

Colony-forming units per swab	*Bacterial species*
More than 0 (Class A)	Group A streptococci *Streptococcus pneumoniae* All Gram negative rods *Neisseria* sp.
More than 10 (Class B)	Alpha-haemolytic streptococci *Staphylococcus aureus* Other micrococcaceae *Branhamella catarrhalis*
More than 100 (Class C)	*Staphylococcus epidermidis* *Bacillus* sp.
More than 10 000 (Class D)	*Corynebacterium* sp. and diphtheroids

[a] According to the criteria of Cagle *et al*[3]

Table 3 Clinical improvement rate: 10 key variables and calculation of clinical improvement

Calculating the clinical improvement rate:

The clinical improvement rate was derived from clinical evaluation scores of the 10 key variables listed below, using a 4-point scale: 0=none; 1=mild; 2=moderate; and 3=severe. The cumulative summary score, used to gauge clinical outcome, was calculated as the sum of the scores for the 10 variables.

Key variables

Lid erythema
Lid oedema
Lid crusting
Palpebral conjunctival hyperaemia
Bulbar conjunctival hyperaemia
Conjunctival oedema
Conjunctival discharge
Corneal oedema
Foreign body sensation
Pain

Clinical outcome

Definition	*Cumulative summary score value*
Resolved	0
Diminished	<baseline and >0
No change	=baseline and >0
Worsened	>baseline or patient discontinued due to lack of drug efficacy

the bacterial infection was either eradicated or controlled.

The clinical improvement rate was defined as the proportion of patients evaluable for efficacy who showed improvement in a cumulative summary score involving 10 key biomicroscopy and symptom variables (Table 3).

Patients were considered to have improved overall if they had improved both clinically and microbiologically. The statistical significance of differences in the clinical, microbiological, and overall improvement rates between the ofloxacin and gentamicin groups was determined by the Cochran-Mantel-Haenszel test, with stratification by investigator.[29] This stratified analysis was completed in an attempt to adjust for differences between investigators at the 18 sites, particularly regarding clinical scoring.

Results

Three of the 194 patients enrolled in the study were disqualified prior to receiving medication. Treatment safety was evaluated in the remaining 191 patients: 93 were treated with ofloxacin and 98 with gentamicin.

Table 4 Demographic profile

	Ofloxacin group	*Gentamicin group*
Age (mean, years)	59·4	54·8
Sex:		
Male	25 (48·1%)	15 (28·3%)
Female	27 (51·9%)	38 (71·7%)
Race:		
White	44 (84·6%)	38 (71·7%)
Black	8 (15·4%)	15 (28·3%)
Iris colour:		
Blue	13 (25·5%)	19 (34·8%)
Green	5 (9·8%)	2 (3·8%)
Brown	27 (52·9%)	29 (54·7%)
Hazel	6 (11·8%)	3 (5·7%)
Data missing	1 (—)	0 (—)

Table 5 Clinical diagnoses

	Ofloxacin	*Gentamicin*
Conjunctivitis	47 (90·4%)	48 (90·6%)
Blepharitis	0 (0%)	2 (3·8%)
Blepharoconjunctivitis	2 (3·8%)	1 (1·9%)
Keratitis	1 (1·9%)	0 (0%)
Keratoconjunctivitis	0	1 (1·9%)
Corneal ulcer	2 (3·84%)	1 (1·9%)

Table 6 Clinical, microbiological, and overall improvement rates in patients treated with ofloxacin or gentamicin

	Number (%) improved		
Drug treatment	*Clinical*	*Microbiological*	*Overall*
Ofloxacin	51/52 (98)	40/51 (78)	40/51 (78)
Gentamicin	48/52 (92)	35/52 (67)	32/51 (63)

There were no statistical differences between the groups in any of the improvement rates, though there was a trend (p=0·089) in the overall improvement results favouring ofloxacin.

Table 7 Microbiological improvement rates for infections involving selected microbial species

	Number of patients		*Percent improved*	
Organism	*Ofloxacin*	*Gentamicin*	*Ofloxacin*	*Gentamicin*
Acinetobacter anitratum	4	4	100	50
Acinetobacter calcoaceticus lwoffi	2	2	100	100
Proteus mirabilis	4	7	100	100
Micrococcus species	6	11	33	54
Pseudomonas aeruginosa	1	2	100	0
Staphylococcus aureus	24	15	88	87
Staphylococcus epidermidis	55	66	87	85
Staphylococcus species	8	11	88	82
Streptococcus viridans	4	3	100	100

A total of 105 subjects ranging in age from 19 to 88 years were considered evaluable for efficacy because of positive baseline cultures. Of these, 25 men and 27 women were assigned by random selection to receive ofloxacin, while 15 men and 38 women were designated for treatment with gentamicin. The two treatment groups were not significantly different with regard to age, race, iris colour, or medical and ophthalmic histories, though there were significantly more women than men in the gentamicin group (Table 4).

A significantly greater proportion of the gentamicin patients presented with a history of corneal disease compared with the ofloxacin group; otherwise, there were no significant differences in clinical diagnoses between the treatment groups (Table 5). Conjunctivitis was the most common diagnosis among the study subjects, accounting for 90% of culture-positive patients. Another 5% of patients were diagnosed with blepharoconjunctivitis and blepharitis. There were no significant differences between the ofloxacin and gentamicin groups with respect to the frequency of specific diagnoses.

Among patients treated with ofloxacin, 98% (51/52) were either clinically cured or improved by day 11, compared with 92% (48/52) of the gentamicin group (Table 6). The signs and symptoms of infection were judged to be completely resolved in 52% (27/52) of the ofloxacin group, compared with 44% (23/52) of the gentamicin group at day 11. There were no notable differences in clinical improvement rates between patients with different baseline diagnoses. Ninety eight percent of ofloxacin-treated subjects with conjunctivitis were found to have improved by day 11, compared with 100% of those with other diagnoses. Among the gentamicin group, 91% and 100% of the patients with conjunctivitis and other diagnoses, respectively, had improved by day 11. None of the differences between the groups showed statistical significance.

MICROBIOLOGICAL IMPROVEMENT

Microbiological improvement was achieved in 78% (40/51) of the ofloxacin patients, compared with 67% (35/52) of the gentamicin group (Table 6), although the difference was not statistically significant. Ofloxacin treatment eradicated the infecting bacteria in 67% (34/51) of patients at day 11, compared with 58% (30/52) after gentamicin treatment. Proliferation occurred in 16% (8/51) of the ofloxacin group vs 27% (14/52) of gentamicin-treated subjects. Nonetheless, all the ofloxacin-treated patients in whom proliferation had occurred were found to have improved clinically as of day 11, compared with 12 of 14 gentamicin patients who had clinical improvement by this time.

Ofloxacin treatment eradicated or controlled 85% (86/101) of the Gram positive organisms and 89% (17/19) of the Gram negative organisms cultured, compared with 83% (103/124) and 78% (29/37), respectively, after gentamicin treatment. In cases involving the most virulent organisms (for example, those with threshold values of 0 as defined by Cagle *et al*[3]), eradication or control was achieved in 87% (14/16) of the ofloxacin patients and in 82% (36/44) of the gentamicin group. Microbiological improvement rates for selected micro-organisms cultured during the study are listed in Table 7.

Disc diffusion sensitivity testing revealed that 2% (4/195) of the Gram positive organisms isolated were resistant to ofloxacin; 11% (22/197) were resistant to gentamicin; and 18% (34/194) were resistant to tobramycin. None of the Gram negative isolates were found to be resistant to ofloxacin or gentamicin; however, 12% (5/41) of the Gram negative isolates were resistant to tobramycin.

Among the ofloxacin patients, 78% (40/51) improved overall – that is, both clinically and microbiologically, compared with 63% (32/51) of gentamicin patients (Table 6). The observed differences in clinical, microbiological, or overall improvement rates between the ofloxacin and gentamicin groups were not statistically significant.

Adverse reactions possibly caused by drug treatment were encountered in three of the 93 ofloxacin patients (3·2%) and seven of the 98 gentamicin patients (7·1%). These reactions, which included burning, stinging, and photophobia, necessitated discontinuation of the drug. No drug treatment related effects on visual acuity, ophthalmoscopic findings, or lens pathology were observed. There was no notable difference between treatment groups in comfort of drug application.

Discussion

The results of this study indicate that 0·3% ofloxacin is an effective, safe, and comfortable treatment for external ocular bacterial infection, primarily conjunctivitis and blepharoconjunctivitis. The clinical, microbiological, and overall improvement rates achieved with ofloxacin were 6%, 11%, and 15% higher, respectively, than those with gentamicin, though statistical significance could not be established.

The clinical and microbiological improvement rates observed in the present study for ofloxacin (98% and 78%, respectively) and for gentamicin (92% and 67%, respectively) are consistent with the results of earlier clinical studies.[2 3 28 30] Mitsui *et al* found that topical ofloxacin produced a good or excellent response in 93% of patients.[28] Cagle *et al* observed clinical cure or improvement in 92% of patients treated with topical gentamicin.[3] Gentamicin yielded microbiological improvement rates of 84% and 74%, respectively, for infections of the conjunctiva and skin-lash margin.[3]

Two percent of Gram positive isolates and no Gram negative isolates were resistant to ofloxacin, which is consistent with previous in vitro reports indicating that strains resistant to this fluoroquinolone do not readily form.[26 27] Since the mechanism of action of ofloxacin involves interference with the supercoiling of chromosomal DNA, rather than a plasmid-mediated process, resistance would not be expected to be easily transferred. In contrast, increasing resistance to the aminoglycosides has been reported.[4 5] In the present study the proportion of Gram positive isolates resistant to gentamicin was approximately five times greater than with ofloxacin. The proportion of Gram positive isolates resistant to tobramycin was nine times greater. Further, a substantial proportion of Gram negative isolates (12%) were resistant to tobramycin, whereas no Gram negative isolates resistant to ofloxacin were observed.

The incidence of side effects owing to ofloxacin was relatively low (3·2%) in our study. A low incidence of side effects (1·1%) was also observed in ofloxacin-treated patients by Mitsui and coworkers.[28]

The present demonstration of the effectiveness and safety of ofloxacin may be at least partially explained by recent animal and human studies showing that effective dosages of this drug are achieved and maintained after topical administration and that the risks of systemic or other side effects is low. In rabbits, tear ofloxacin levels exceeded the minimal inhibitory concentration against 90% of bacterial strains tested in vitro (MIC$_{90}$) for 4 hours after topical application, whereas gentamicin levels remained higher than the MIC$_{90}$ against Gram positive organisms for only 20 minutes and the MIC$_{90}$ against Gram negative organisms for only 120 minutes.[31] In addition, 4 hours after topical application, mean ofloxacin levels in human tear film (9·16 (SD 8·24) μg/g)[31] were higher than the MIC$_{90}$ (2 μg/ml) for ofloxacin reported in the literature.[24]

In another study, topical 0·3% ofloxacin ointment produced higher tear concentrations for a longer period than did an aqueous solution of the drug.[33] The highest tear level obtained with the ointment was detected within 30 minutes, and effective concentrations were present 60 minutes after administration.

The fluoroquinolone, ofloxacin, is a promising new agent for treating external ocular infection and may prove especially valuable in cases that are difficult to manage because of resistance to standard agents now in use.

Results of this study were presented as a poster at the annual meeting of the American Academy of Ophthalmology, October 1989.

This study was sponsored by Allergan, Inc, Irvine, California. Allergan is investigating the clinical utility of topical ofloxacin in the treatment of ocular infections.

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Contrast sensitivity and glare in cataract using the Pelli-Robson chart

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Abstract

There is a need for a convenient, clinically applicable test of glare disability which can be used in the preoperative evaluation of patients with cataract. In this study, contrast sensitivity (using the Pelli-Robson letter chart), near vision, and visual acuity were compared, with and without the introduction of a glare source in 70 patients with cataract, 15 with intraocular lenses, and 19 controls. A disposable pen torch was shone at the pupillary margin to induce glare. Contrast sensitivity demonstrated the most marked reduction during glare testing. Cortical cataracts were most affected followed by posterior subcapsular opacities. The glare disability was significantly less in pseudophakic patients and was absent from patients with non-cataractous phakic eyes. Glare testing with a disposable pen torch and a Pelli-Robson contrast sensitivity letter chart provides a rapid test of glare disability which can be easily incorporated into the clinical appraisal of patients with cataract.

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A discrepancy is often encountered between the visual function measured by Snellen acuity and the visual disability that is experienced by patients with cataract.[1] The disparity has become more apparent as the reliability, acceptability, and success rate of cataract extraction and intraocular lens implantation has improved. A measurement of visual disability by Snellen acuity alone is now less than satisfactory and additional tests of visual deficit and postoperative improvement are required.

Contrast sensitivity and glare disability are sensitive measurements of visual loss in patients with cataract, particularly those with mild or moderate lens opacities. Investigators using computer based monitor systems[1-3] or projection devices[4] have demonstrated a reduction in contrast sensitivity in these patients. Paulsson and Sjostrand[3] also tested the effect of glare on contrast sensitivity by placing a bright light source adjacent to a VDU displaying sinusoidal gratings and Abrahamsson and Sjostrand have used a TV monitor surrounded by a fluorescent tube for this purpose.[5,6] These tests are sensitive measures of visual function but they are laborious to perform. The incorporation of these testing methods into routine practice would require the purchase of expensive equipment. If a test is to be used regularly in the clinic it is essential that it is quick, reproducible, and readily available. In this study, we report the results obtained by using a Pelli-Robson letter based chart to test contrast sensitivity and a disposable pen torch as the glare source. This test is simple and rapid, and could be easily introduced into a busy clinical environment.

Patients and methods

Subjects with cataract were recruited from patients attending the Department of Ophthalmology at Addenbrooke's Hospital, Cambridge. Patients with high myopia or ocular disease other than cataract were excluded.

All subjects were questioned as to the extent of their symptoms for near vision, distance vision, and glare disability and asked to rank these on a six point scale.

Snellen visual acuity was tested using a standard back illuminated Snellen chart at 6 m. The appropriate spectacle correction was worn and the visual acuity was rounded off to the nearest line.

Jaeger plates were used to test near vision at 0·3 m with a reading correction.

Contrast sensitivity was tested with a Pelli-Robson chart.[7,8] This chart consists of letters of constant size arranged in 16 groups of three. The contrast of all the letters in the first of these triplets is 100%. The contrast of each subsequent triplet is reduced by a factor of 0·707 (0·15 log unit). Thus the contrast of the last triplet is 0·56% (2·25 log units below 100%). The chart was used at 1 m at a mean luminance of 65 cd/m^2 as recommended by the suppliers.

Glare was introduced with a disposable pen torch which was held at 20 degrees to the visual axis at 30 cm from the eye and directed at the pupil. At this distance the pen torch has a mean luminance of 4000 cd/m^2. Snellen acuity, Jaeger near acuity, and Pelli-Robson contrast sensitivity were tested without and then with the pen torch glare. The pen torch was replaced after every five patients. The pens were tested with a photometer which confirmed that there was no loss of brightness with this amount of usage.

The lens opacity of each cataract patient was graded for type (posterior subcapsular, nuclear, cortical, or mixed) and for severity (on a three point scale).

STATISTICAL METHODS

For the purpose of statistical analysis the Snellen and Jaeger acuities were converted to equivalent value of visual angle using the decimal scale in which 6/6 has the value of 1·0, 6/12 the value 0·5, 6/60 the value 0·1, and so on. The effect of glare upon vision for near (J-diff) or distance (VA-diff) was expressed as the difference between the logarithms of the values obtained with and without glare. As the Pelli-Robson chart gives a logarithmic measure of contrast sensitivity the effect of glare upon contrast sensitivity (CS-diff) was obtained directly by subtraction.

A multivariate analysis using Rosner's intraclass correlation model was performed. This is the most efficient statistical method for the analysis of studies with a two eye design and continuous dependent variables. The method avoids the overestimation of significance levels which occurs if individual eyes are regarded as independent units of observation. The analysis was performed using the Generalised Linear Interactive Modelling (GLIM) system of the Numerical Algorithms Group (Wilkinson House, Jordan Hill Road, Oxford, OX2 8DR). In the analyses eyes were classified by lens status into groups and subgroups according to cataract type (cortical, posterior subcapsular, nuclear, and mixed), pseudophakia, and phakic non-cataractous controls.

Results

PATIENT CHARACTERISTICS

The mean age of the group with cataract was 72·8 years (SD 9·4, range 44–91); of the pseudophakic patients was 72·9 years (SD 9·4, range 64–86); and of the non-cataractous phakic controls was 60·9 years (SD 10·0, range 44–76).

In the cataract group there were 105 eyes in 70 patients; in the pseudophakic group there were 15 eyes in 15 patients; and in the control group with clear lenses there were 34 eyes in 19 patients. The 105 eyes with cataract were further divided into subgroups by cataract morphology such that there were 17 eyes with cortical cataract, 28 eyes with posterior subcapsular cataract, 37 eyes with nuclear cataract, and 23 eyes with mixed cataract morphology.

SNELLEN VISUAL ACUITY. JAEGER VISION AND CONTRAST SENSITIVITY

There were no significant differences between the visual acuities without glare in the four cataract subgroups (p=0·09). Without glare, Snellen acuity correlated well with contrast sensitivity (r=0·74), Jaeger acuity correlated well with contrast sensitivity (r=0·73), and Snellen acuity correlated well with Jaeger acuity (r=0·75). Despite these apparently good correlations between the various measures of visual function, there remains considerable spread about the regression line between these variables. This is exemplified graphically in Figure 1, where it can be seen that for a given Snellen acuity there remains quite a wide range of contrast sensitivity.

GLARE EFFECT

The pen torch glare effect was regarded as the difference in visual function measured with the glare source off and on. The effect of glare on visual function was examined in the groups with cataract, pseudophakia, and clear lenses, as well as in the four cataract subgroups.

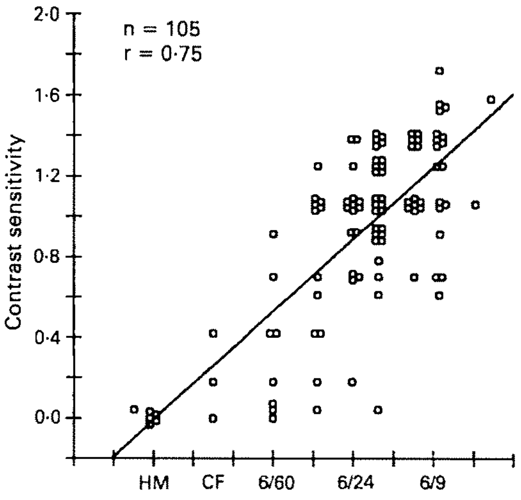

Figure 1 Contrast sensitivity versus Snellen acuity (both on a log scale) prior to surgery for all the patients in the study.

When the effect of glare upon contrast sensitivity was compared between the different types of cataract there were significant differences between these groups (p=0·0025). The subtype of cataract producing the greatest loss of contrast in response to glare was the cortical, followed in reducing order by posterior subcapsular, mixed, and nuclear cataract.

There were no differences in the glare effect upon Snellen acuity between the cataract subgroups, pseudophakic, or control subjects (p=0·34). The glare effect upon Jaeger vision, however, was not uniform across these groups (p=0·045). The difference in performance was accounted for by the non-cataractous phakic controls, who were less affected by glare than the cataractous and pseudophakic subjects. Compared with the controls the other subgroups were affected from most to least in the order: posterior subcapsular cataract, mixed cataract, cortical cataract, nuclear cataract, and pseudophakia (Table 2). Differences within this rank ordering however were not significant (p=0·13).

There were marked differences in the glare effect between the groups and subgroups with regard to contrast sensitivity ($p<10^{-6}$). This powerful effect was mainly due to differences between the non-cataractous phakic controls and the other groups. There was a significant difference between the pseudophakic subjects and the non-cataractous controls (0·005), the pseudophakic subjects suffering a more marked loss of contrast sensitivity than the controls. The pseudophakic subjects experienced slightly less loss of contrast sensitivity than the subjects with cataracts (Table 3), though this effect was statistically non-significant (p=0·14).

SYMPTOMS

Snellen acuity and visual symptoms at distance showed a strong association ($p<10^{-6}$) and symptoms of reading difficulty correlated similarly with Jaeger vision ($p<10^{-6}$). However symptoms of glare difficulty were not significantly associated with the effect of glare upon Snellen acuity (p=0·20), Jaeger acuity (p=0·71), or contrast sensitivity (p=0·61).

Table 1 The mean distance visual acuity for each of the groups, with and without glare, and the mean effect of glare. (All data on a linear scale)

Type	*With glare*	*Without glare*	*Difference*
PSCLO*	0·354	0·374	0·0196
Nuclear	0·326	0·340	0·0142
Cortical	0·431	0·436	0·0049
Mixed	0·276	0·292	0·0160
IOL†	0·606	0·630	0·0240
Control	0·887	0·887	0·0000

*Posterior subcapsular lens opacity.
†Intraocular lens.

Table 2 The mean Jaeger near acuity for each of the groups, with and without glare, and the mean effect of glare. (All data on a linear scale)

Type	*With glare*	*Without glare*	*Difference*
PSCLO	0·148	0·200	0·0515
Nuclear	0·194	0·222	0·0275
Cortical	0·221	0·283	0·0620
Mixed	0·122	0·181	0·0590
IOL	0·306	0·329	0·0227
Control	0·354	0·354	0·0000

Table 3 The contrast sensitivity for each of the groups, with and without glare, and the mean effect of glare

Type	*With glare*	*Without glare*	*Difference*
PSCLO	0·701	0·991	0·2896
Nuclear	0·690	0·861	0·1705
Cortical	0·154	0·660	0·4941
Mixed	0·560	0·777	0·2161
IOL	0·991	1·143	0·1519
Control	1·453	1·453	0·0000

Discussion

As demonstrated by Figure 1, contrast sensitivity for a given visual acuity varies quite widely between patients. CS loss, therefore measures a different visual disability compared with loss of Snellen acuity and can provide the clinician with added information concerning the extent of visual disability.[1] This is especially the case in patients whose visual acuity remains good despite significant lens opacities. Contrast sensitivity drops as the severity of the cataract increases and improves markedly after cataract extraction and lens implantation.[9]

Patients with cataract often complain about glare – for example, from bright sunlight or car headlights, and may find this glare more disabling than a moderate drop in visual acuity. These symptoms have been termed glare disability[5 10] and are due to increased intraocular light scatter and subsequent loss of contrast of the retinal image. Attempts have been made to provide clinically applicable tests of glare. For instance Prager *et al* measured Snellen acuity under office light compared with that in sunlight as a measure of glare[11] and Maltzman used a pen torch to provide glare whilst measuring Snellen visual acuity.[12] However Snellen acuity is little affected by loss of contrast so these tests can be expected to be insensitive. Our finding of a much more marked effect of glare upon CS than either Snellen acuity or Jaeger near vision suggests that CS is a substantially more sensitive measure of glare disability than the other two tests.

We did not find a correlation between the subjective symptoms of visual glare and the measured effect of glare upon contrast sensitivity. This may reflect the difficulty of devising a meaningful scoring system for subjective glare disability. Different patients may have rated the same degree of glare disability quite differently.

All forms of cataract showed glare disability. In keeping with common clinical experience posterior subcapsular lens opacities showed severe glare loss. However the marked extent to which glare also affected the patients with cortical lens opacities was unexpected.

After cataract extraction and intraocular lens implantation the glare disability is much reduced but an effect of glare is still demonstrable.[13–15] In the present study the patients with extracapsular cataract extraction and posterior chamber lens implantation had a mean reduction in CS owing to glare of 0·152 (Table 3) yet the control group was found to have no loss owing to glare at all. This glare disability in pseudophakia may be attributable to light scattering either by the posterior capsule or by the intraocular lens.

The advantages of contrast sensitivity and glare disability measurements in the clinical setting can be illustrated by the following case. A 23-year-old male, who worked as a labourer, presented complaining of difficulty seeing in bright light. He wore sunglasses when he worked outdoors but these brought only partial benefit and he was unable to read a number plate at 25 yards in daylight and thus unable to drive. He was found to have congenital cataracts, more marked in the right eye, and had already undergone a right lensectomy 3 years previously. Unfortunately, the visual acuity in this eye improved only to 6/36 with contact lens correction because of the presence of stimulation deprivation amblyopia. The visual acuity in the left eye was 6/6 with appropriate refractive correction but the contrast sensitivity on the Pelli-Robson chart was only 0·80 (normal range 1·65–1·89 for a 20–30-year-old). This became unrecordable in the presence of the glare light. A snowstorm punctate type of congenital cataract was present in the left eye.

Many surgeons would have been reluctant to carry out a cataract extraction and lens implant on this patient in view of the good visual acuity. However accurate measurements of the visual deficit by contrast sensitivity and glare disability strongly supported the decision to operate. The patient therefore underwent cataract extraction and lens implantation and subsequently a YAG capsulotomy. The postoperative visual acuity was 6/6 and the contrast sensitivity improved to 1·65 and did not deteriorate with glare. The patient is now able to work without any difficulty and is planning to take his driving test.

This study shows that the Pelli-Robson chart is a much more sensitive means of demonstrating glare disability than Snellen or Jaeger acuity. Using the chart and a pen torch it is possible to show in patients with cataract that contrast sensitivity is reduced by glare to a much greater extent than in normal controls. The Pelli-Robson chart is both convenient and quick to use. It is easy for the patient to perform and the observer to interpret. In this study it was found to be a useful clinical test of contrast sensitivity and glare disability in patients with cataract. This test may prove particularly useful in those patients whose complaints are out of proportion to their Snellen acuity.

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Refraction changes in children developing convergent or divergent strabismus

Maths Abrahamsson, Gerhard Fabian, Johan Sjöstrand

Abstract

Strabismus and amblyopia were studied in a cohort of children born in 1979 or 1980 in the area of Västerås, Sweden. Forty percent of the children had participated in a voluntary eye examination at 1 year of age. All children diagnosed as strabismic and/or amblyopic between 1979 and 1988 at any of the three eye clinics in the area were included in this study. Strabismic cases were mostly detected by the parents while microstrabismus and straight eye amblyopia were found at the general 4 years of age screening at children's health centres. In 57 cases with (n=31) and without amblyopia (n=41) it was possible to obtain several refraction values between 1 and 6 years of age. In this study we concentrated on manifest esotropia and exotropia. The aim of the study was to describe changes of refraction before and after onset of strabismus and to establish risk indicators that identified populations at risk of developing strabismus. We found that patients with esotropia show a more pronounced hypermetropia than exotropic cases at the time of detection of strabismus. This difference becomes more definite over time, since hypermetropia increased in the deviating eye in the esotropic cases while refractive errors remained stationary in most of the exotropic eyes. It was also apparent that anisometropia frequently developed after onset of strabismus in esotropic cases in contrast to exotropic cases. An increasing refractive error in the deviating esotropic eye could be combined with an emmetropisation of the fixating eye.

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During the past two decades there has been a focus of interest on the changes of refraction during infancy and childhood. Previously it was believed that infants were hypermetropic at birth and that there was a decrease in hypermetropia during infancy and childhood. Later it was determined that as many as 20% of the newborn are myopic.[1 2] Other studies have shown that after the infantile period (at 1 or 2 years of age) most children are hypermetropic.[1 3] From the age of approximately 1 year there is a decrease in refractive errors, especially in the amount of astigmatism.[3-5] These data together with other studies indicate that there are considerable changes in refraction during the first years of life.[6-8]

One reason for this growing interest is the possibility of using refractive errors as risk indicators useful in screening programmes for young children in order to prevent amblyopia and squint. Knowledge of potentially dangerous refractive anomalies is necessary in order to define the population at risk. The high variability of the individual refraction during early childhood complicates the determination of risk indicators. Age becomes an essential factor for evaluation of when a refraction error is potentially detrimental for visual development.

In this study we were interested in the refractive changes of children who develop strabismus. In patients with convergent strabismus we have known that there is a relationship to hypermetropia since 1864 when Donders presented his publication 'On the anomalies of accommodation and refraction of the eye.' This has later been confirmed by several studies (cf Duke Elder).[9] The longitudinal changes of refraction in esotropic individuals have also been studied,[10-12] and one study has examined refractive changes before the onset of strabismus.[11] Though these studies[9-12] all found a high hyperopia in most cases with esotropia it is still difficult to determine a refraction limit at any particular age that separates potentially esotropic children from normal ones.

In divergent strabismus, early studies by Donders indicated an association with myopia. This relationship was questioned however at the beginning of this century.[9] There seems to be a portion of myopia among the exotropic children but the majority are hypermetropic at onset.

The aim of this study was to compare refraction changes in children with manifest esotropia or exotropia compared with the development of the refractive errors in normal children. We also wanted to examine refractive changes before and after the onset of the strabismus to detect whether abnormal refractive behaviour could be used as an indicator for pointing out patients at risk of developing strabismus and/or amblyopia.

Methods

SUBJECTS

Refraction data for the study were obtained by combining two different studies. In the first we examined, motility, fixation, refractive errors, and heredity of 9000 children at 1 year of age. These children took part in a voluntary ophthalmic examination (1971–81). The examination was offered through children's health care centres to all children in the city of Västerås, Sweden. Approximately 50% of the children born in the area took part in the examination.

In the second study we scrutinised the hospital files of all children born between 1979 and 1980 who visited one of the three ophthalmic clinics in the city of Västerås, Sweden, during the 1980s. We found 715 cases that for some reason visited an eye clinic before 8 years of age. There were a

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Table 1 Distribution of strabismus

	Esotropia	*Exotropia*	*Microtropia*	*Infantile*	*Paralytic*	*Total*
Number of patients	41	21	8	6	4	80
Percentage of strabismic patients	51	26	10	8	5	100
Percentage of all children born in the area 79, 80	1·4	0·7	0·3	0·2	0·1	2·7

large variety of reasons for the visits. Most common were conjunctivitis, trauma, strabismus, or suspected amblyopia. In 290 of these patients we have refraction data from the voluntary examination at 1 year of age that could be analysed together with data from the first visit to an eye clinic. In 57 cases with strabismus (n=31) and/or amblyopia (n=41) it was possible to obtain a series of refraction values between 1 year of age and up to 5 or 6 years of age.

The patients were refracted by retinoscopy 30 minutes after instillation of cyclopentolate (1%). Spectacles were prescribed at detection of the strabismus in patients with hypermetropia ≥ 2D. The anisometropia of the strabismic and amblyopic patients was fully corrected. None of the amblyopic and/or strabismic cases wore spectacles before detection of strabismus/amblyopia. Time of detection was defined as the date when strabismus is diagnosed by an ophthalmologist or by an orthoptist.

In this study we describe refraction and refraction changes and their significance in patients with manifest strabismus. The reliability of the data depends on the accuracy of the refraction data and ability of the screening programme to detect patients with amblyopia and strabismus and refer them to an eye clinic. In our earlier studies all refraction determinations have been done by one ophthalmologist (GF) with much experience of refraction determination in young children.[1 3 13 14] All refraction measurements with young children were performed by GF while some refraction data in older children were obtained from several other ophthalmologists at different eye clinics. We are aware of the problem of having several ophthalmologists involved and have tried to minimise the effects.

We have chosen to follow longitudinal changes in refraction from 1 to 4 years in the majority of cases. The reason for choosing 4 years as an endpoint is that we have a general health screening in Sweden at the age of 4 years. More than 95% of all children take part in that screening. Studies indicate that most amblyopic cases that are not previously known are identified at this screening.[15 16]

STRABISMUS AND AMBLYOPIA

The cases of manifest strabismus (n=80) were classified into one of five categories; esotropia, exotropia, microstrabismus, infantile, and paralytic strabismus (Table 1). Infantile strabismus was defined as a manifest strabismus detected before 9 months of age. All patients with predominantly intermittent strabismus were excluded from the study. We concentrated especially on the cases with esotropia and exotropia. The cases with infantile esotropia and microstrabismus were not included in the comparison of refraction changes (Figures 4 and 5).

Straight eye amblyopia and microstrabismus are generally detected by the Swedish general health screening[15] and cases with strabismus are referred to an eye clinic by the children's health care centres. Children with monocular visual acuity lower than 0·8 or an interocular difference in acuity of two rows or more (HVOT or tumbling E letter chart) at the 4 year screening are retested within the screening programme. Children with subnormal vision at both these test sessions are referred to an eye clinic. We have chosen to use a somewhat uncommon definition of amblyopia in our analysis of the hospital files. A patient must fulfil the following two criteria in order to be classified as amblyopic: (1) an acuity difference (approximately 0·1 log unit or more, which equals 1 line or more) between the eyes measured at the eye clinic with best correction at least two separate consecutive test sessions in eyes with no signs of disease; (2) the acuity of the 'amblyopic' eye improved at least one line following the occlusion treatment.

The first criterion means that a child will have his visual acuity tested four times before he or she is classified as amblyopic if referred from the general health screening programme. Children referred from sources outside the screening programme pass two visual acuity tests or more before they are classified as amblyopic. The amblyopic cases (n=126) were classified into

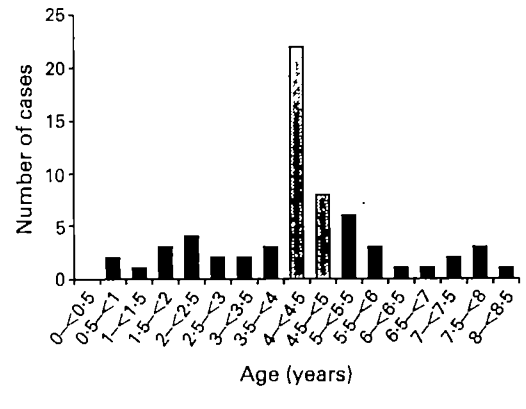

Figure 1 The age at which amblyopia is diagnosed by an ophthalmologist at an eye clinic in the city of Västerås, Sweden, is presented for all children born in 1979 or 1980. The hatched columns indicate those children with amblyopia identified by the screening programme at approximately 4 years of age.

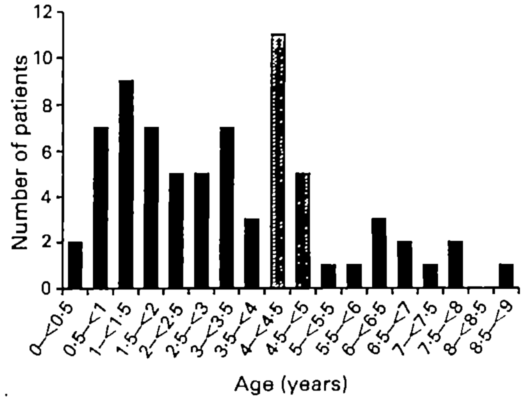

Figure 2 The age at which strabismus is diagnosed by an ophthalmologist is presented for all children born in 1979 or 1980 and visiting an eye clinic in the city of Västerås, Sweden. In the diagram both manifest and intermittent strabismus are included. The hatched columns indicate those children with strabismus (mainly microstrabismus) identified by the screening programme at approximately 4 years of age.

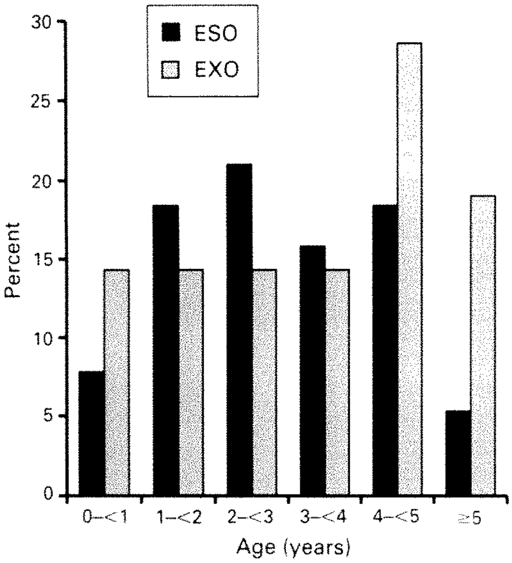

Figure 3 The relative distribution of the age at detection of cases with manifest strabismus is presented for children with esotropia and exotropia respectively. The column 0–1 year contains only cases detected between 9 and 12 months of age.

three different groups according to the severity of the visual loss. The best corrected visual acuity (VA) of the amblyopic eye at the start of treatment was graded in three levels as follows: VA ≤0·2, 0·2<VA≤0·5, and VA >0·5.

Results

In Swedish children there are different patterns for detection of strabismus compared with amblyopia. Cases with amblyopia without eye deviation or with microstrabismus are mostly identified by the visual screening programme. All (>95%) of the Swedish children have a general health examination, including an eye examination, at 4 years of age. In Figure 1 the age at detection of amblyopia is presented. The cases identified earlier than 4 years of age usually have large angle strabismus or amblyopia caused by visual deprivation (that is, infantile cataract, ptosis). The detection pattern of strabismus is different (Fig 2). The age of detection is evenly distributed between 1 and 4 years. The screening programme identifies undetected microstrabismic cases while cases with manifest large angle strabismus are identified by the parents. These cases are referred by the children's health centre to an ophthalmologist shortly after onset of the strabismus. In Table 1 the distribution of the different types of manifest strabismus is presented both as numbers and as a percentage of patients found in hospital files, and as a percentage of all children born in the area. Approximately 75% of all cases with strabismus were classified as exotropia or esotropia. Infantile, paralytic, and microstrabismus represented approximately one quarter of all strabismus diagnoses. The ratio between number of cases with convergent and divergent strabismus was approximately 2:1.

REFRACTION AND REFRACTION CHANGES

For the study of refraction we have concentrated our analysis of the refraction changes with time in cases with manifest esotropia and exotropia (n=62, Table 1). No cases of infantile strabismus (detected earlier than 9 months of age), paralytic strabismus, microstrabismus, or predominantly intermittent strabismus were included. The age at detection of the two types of strabismus is presented in Figure 3. The onset of esotropia and exotropia is distributed differently. Most (≈95%) esotropic cases are detected between 1 and 4 years of age while more than 40% of the exotropic cases are detected later than 4 years of age.

At the time of detection of strabismus, astigmatism (≥1·0 D) is common (29% of all cases) in both eyes in both convergent and divergent strabismus while anisometropia is more uncommon in both esotropia and exotropia (esotropia n=5/41; exotropia n=3/21). The distribution of the refractive error (spherical equivalent) in the deviated eye at detection, however, is different between the two groups of strabismus (Fig 4). More than 60% of the esotropic patients have a hypermetropia that is more than 2 dioptres in the deviating eye at the date of detection while we found no case with myopia in this group. It is notable that in seven (18%) of the esotropic cases the refractive error was less than 1 dioptre in any meridian. In exotropia larger refraction errors are more

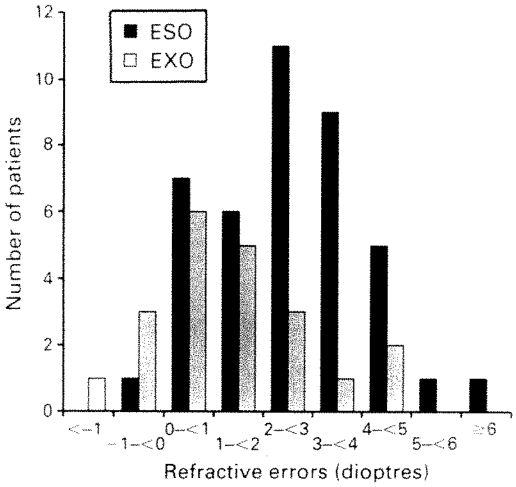

Figure 4 The refraction error for the deviating eye at the age of detection is presented for children with manifest esotropia and exotropia respectively. Since the anisometropia was present in approximately 10% of the cases the refractive error of the fixing eyes is approximately the same as the refractive error of the deviating eye.

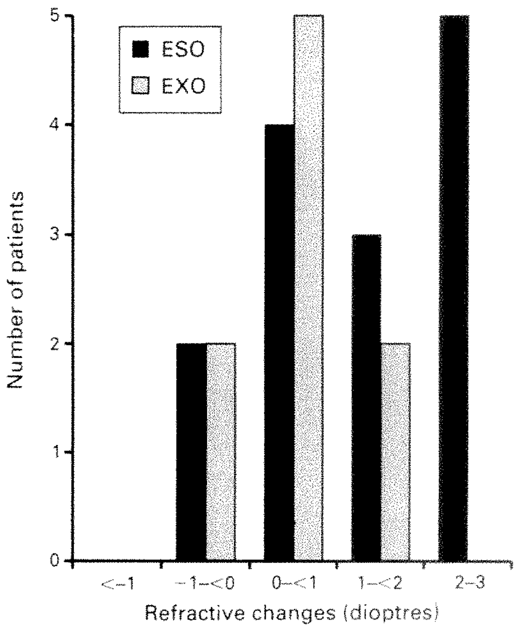

Figure 5 The longitudinal changes in refraction of the deviating eye of children with manifest esotropia and exotropia respectively. The refraction changes are calculated as spherical equivalent at 4 years of age minus spherical equivalent at 1 year of age.

Table 2 Distribution of amblyopia

	VA≤0·2	*0·2<VA≤0·5*	*0·5<VA*	*Total*
Number of patients	11	46	69	126
Percentage of amblyopic patients	8·7	36·5	54·8	100
Percentage of all children born in the area 79, 80	0·3	1·5	2·3	4·1

uncommon. In 65% of the cases the errors are between −1 and +2 D in the deviating eye. One exotropic patient has a pronounced myopia (−8 D) in both eyes.

In order to study differences of refractive errors in the deviating eye at onset two age groups were compared: children younger than 36 months at onset (but older than 9 months) and older than 36 months. No significant difference in the distribution of refractive error in convergent or divergent squint respectively could be found for the two age groups. The same differences between exotropia and esotropia as described above were thus found in both age groups.

The refractive changes between 1 and 4 years of age could be studied in 23 cases with nonalternating strabismus, 14 esotropic (14/41), and nine exotropic (9/21) patients (Fig 5). At 1 year of age one esotropic and two exotropic patients are myopic and five esotropes and three exotropes had a hypermetropia greater or equal to 3·5 D in the most hypermetropic meridian in any eye. The majority of the esotropic patients (10/14) show an increase in hypermetropia ≥0·5 D in the strabismic eye during the period from 1 to 4 years. Increasing hyperopia could be identified both before and after the detection of the esotropia in more than 50% of the deviating eyes while in several cases there was an emmetropisation or at least a decreasing hypermetropia in the fixating eye. In the esotropic patients anisometropia developed owing to this difference in behaviour between the eyes. At 1 year of age as well as at onset of the esotropia there is one (1/14) case with anisometropia. One year after onset (11–16 months) 13 of the esotropes had developed anisometropia greater or equal to 1 D. Most patients with divergent squint showed small (≤0·5 D) or no changes in the refraction in either eye (7/9). The same process of developing anisometropia as in convergent squint could not be seen.

STRABISMUS AND AMBLYOPIA

The distribution of acuity of all amblyopic eyes is presented in Table 2. We used the amblyopia definition presented in the Methods section and classified the patients into different groups according to the severity of the visual loss. In more than 50% of the cases with amblyopia the visual acuity in the amblyopic eye was better than 0·5. When we combine the distributions of amblyopia and strabismus (Tables 1 and 2) in the whole population we found that in our estimation of distribution 2·7% of all children had strabismus and 4·2% had amblyopia, while the percentage with both amblyopia and strabismus was 1·4%.

Amblyopia was present in 53% of all the cases with manifest strabismus (42/80) while patients with squint represented 33% of all amblyopic cases (42/126). When we study only severe amblyopia (VA <0·2) the relationship between amblyopia and strabismus is much more pronounced: 72% of the patients with severe amblyopia were also squinting (8/11). The distribution of convergent and divergent strabismus into different amblyopia categories was very similar. Approximately 20% in both groups of strabismus developed severe amblyopia (VA <0·2). The same was true for microstrabismus while all cases of paralytic strabismus presented with amblyopia of a low magnitude (VA >0·5). The number of patients is small so these data can suffer from random errors.

The treatment for amblyopia was unsuccessful in six cases out of 80 (7·5%) with strabismus. Unsuccessful means a difference in acuity of two rows or more after the conclusion of the occlusion treatment. Five of the cases who remained amblyopic despite treatment had convergent squint, and in only one case was a divergent squint present. That child also had nystagmus. Among the five children with esotropia and amblyopia persisting after treatment two cases had severe amblyopia.

Discussion

There is a limited knowledge of the causes of manifest squint. However, in some cases the general mechanisms that produce the squint are known. Brain damage, neuromuscular anomalies, and abnormalities of the fusion mechanism are related to motor problems that can cause squint. Strabismus can also be caused by mechanical factors in the orbit. Finally there is an established relationship between accommodation, refraction, and concomitant squint. Several studies have pointed out that hypermetropia and anisometropia are overrepresented in cases with convergent squint.[11 12] In our study we found that almost two thirds of the esotropes had hypermetropia (spherical equivalent) – that is, over 2 D in the deviating eye – whereas only 7% had anisometropia at onset. The relationship between hyperopia and esotropia is most probably causal in many of the cases. There is a plausible aetiological connection through accommodation and the strabismus may be cured by correcting the refraction error.

The relationship between ametropia and the development of strabismus is discussed in most textbooks. Both anisometropia and hypermetropia, as well as pronounced astigmatism, have been said to trigger the development of strabismus owing to disturbances of fusion. More recent studies[17] have pointed out meridional hypermetropia of +3·5 or more in a child at 1 year of age as a useful risk indicator both for amblyopia and strabismus. In our study we found that five of 14 cases with esotropia had a hypermetropia of +3·5 or more at 1 year of age. This number has increased to seven of 14 esotropes at onset of the strabismus. The connection between age and refractive error has proved to be ever more interesting, since there is a high variability and change in refraction during the first years of life.[1 3 4 5 8 18] In earlier studies we found that in certain cases more than 4 dioptres of astigmatism and anisometropia may disappear during the period 1 of 4 years.[3 13 14]

In this study we found that most of the children before onset of their convergent squint had a hypermetropia of >2 D or more in the deviating eye at 1 year of age while it was uncommon with hypermetropia ≥2 D at the same age in the deviating eye in cases with future divergent squint. In a normal control eye the refractive error should have decreased to 1–1·5 D at the age of 4 years. Studying the refractive error at 4 years we found a very limited decrease in refraction of the deviating eye of both groups (Fig 5). Among the convergent squinters there was even an increase in the refractive error in most cases, with as much as 2·75 D in one case. If esotropia was characterised by an increasing refractive error divergent squint was characterised by a lack of emmetropisation of the deviating eye. In most of the exotropic cases there was no change in refraction at all during the test period of 1 to 4 years.

A most interesting finding was that some esotropic cases developed anisometropia after the onset of the strabismus. Seven percent of the esotropes had anisometropia at onset which could be compared with the 10% we found for the whole population at that age level[13] (and unpublished data). Among the 14 esotropic cases which could be followed with respect to refraction between 1 and 4 years one case had anisometropia at onset of strabismus. At 1 year after (11–16 months) onset 13 of 14 children had developed anisometropia. This tendency to develop anisometropia following onset in esotropic patients can also be seen in other studies of longitudinal changes in refraction in the deviating eye before and after onset of strabismus.[10 11] In our study anisometropia was found in all but one case of convergent strabismus at 1 year after the onset of the squint. Detailed study of the refractive changes indicates that the anisometropia is created owing to the fact that the fixating eye is emmetropising, while this process is interrupted in the deviating eye. We even found increasing refractive errors in the deviating eye. Data from Aurell and Norrsell[11] indicate disturbances in the emmetropisation process in both eyes before the onset of the esotropia in children with a family history of strabismus. Since our data are collected without a specific time schedule for the testing it is impossible to calculate any mean difference in time between the onset of strabismus and the onset of anisometropia. Among the patients with divergent squint no case could be demonstrated with anisometropia developing after the onset of the squint.

In a study of the relationship between refraction and amblyopia[14] we found that an increasing refractive error between 1 and 4 years of age was related to the development of amblyopia in cases without deviation. The same seems to be true for the development of convergent strabismus. In this study we found that no child developed esotropia which had a decreasing refraction in the deviating eye before onset. Development of esotropia without anisometropia at onset was the most common finding. After onset we found cases with anisometropia and esotropia without amblyopia but no case with amblyopia and esotropia without anisometropia among those cases longitudinally followed. It is known that one can have anisometropia and amblyopia without esotropia. From those findings one may conclude that both esotropia and amblyopia are strongly associated with anisometropia; the combination of these particular conditions has the potential to cause anisometropia.

In divergent squint refraction seems to be neither a cause nor a risk indicator. We found no relationship between refraction and refraction changes and the development of divergent strabismus.

In conclusion, there is evidence that convergent and divergent squint are caused by different mechanisms. Refraction changes between 1 and 4 years of age characterised by failure of emmetropisation are observed both in cases developing convergent strabismus or amblyopia without any deviation. Anisometropia is mainly a secondary phenomenon in convergent squint while it can be a primary condition in divergent squint.

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Magnetic resonance imaging of the optic nerve in extremes of gaze

Implications for the positioning of the globe for retrobulbar anaesthesia

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Abstract

Orbital magnetic resonance imaging was carried out in nine directions of gaze in a normal subject. The findings are presented and discussed especially in relation to retrobulbar injections. Atkinson's position is confirmed to be hazardous and a new position for the globe at retrobulbar injections is suggested.

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With the advent of day case surgery, a larger proportion of intraocular surgery will be performed under local anaesthesia.[1] Though cataract surgery could be performed with peribulbar or even subconjunctival anaesthesia alone, many surgeons in Great Britain and in the United States still use a retrobulbar block.[2]

As retrobulbar anaesthesia involves blind insertion of a needle it is not surprising that accidental damage to orbital structures should occur from time to time. The possible complications of retrobulbar injections are well known and range from perforation of the globe, retrobulbar haemorrhage, and injection into or occlusion of orbital vasculature, to damage to the optic nerve (ON).[3-5] The latter is probably much more common than is recognised as it is not routinely looked for. However, the most hazardous complication is injection of anaesthetic agents into the subdural space of the optic nerve,

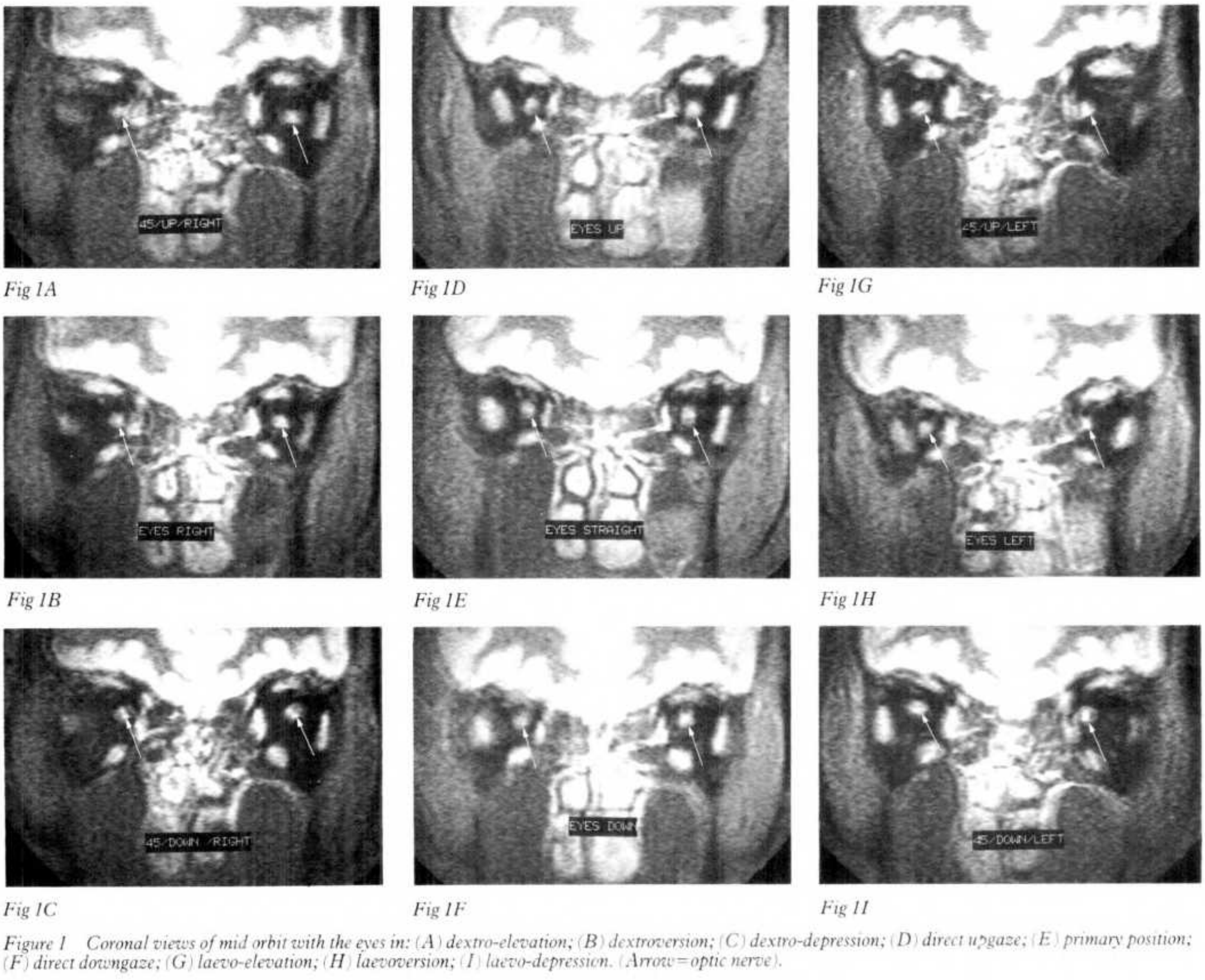

Fig 1A *Fig 1D* *Fig 1G*

Fig 1B *Fig 1E* *Fig 1H*

Fig 1C *Fig 1F* *Fig 1I*

Figure 1 Coronal views of mid orbit with the eyes in: (A) dextro-elevation; (B) dextroversion; (C) dextro-depression; (D) direct upgaze; (E) primary position; (F) direct downgaze; (G) laevo-elevation; (H) laevoversion; (I) laevo-depression. (Arrow = optic nerve).

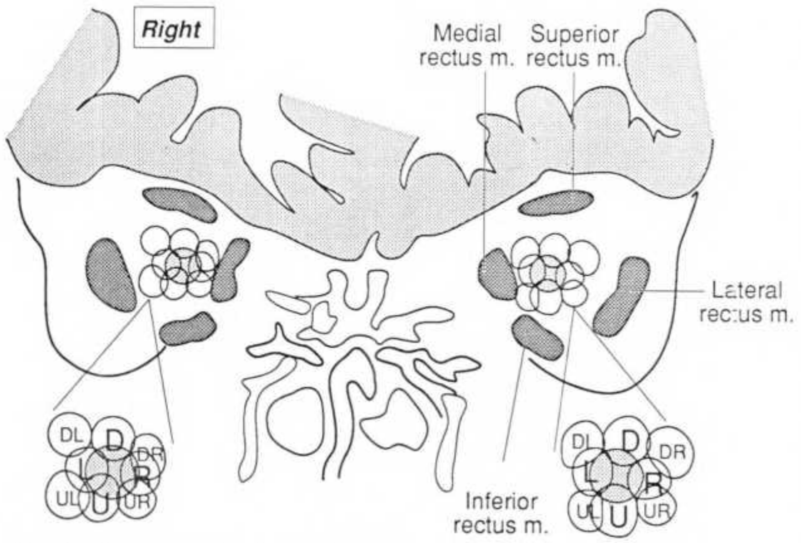

Figure 2 Composite tracing of coronal sequences.

causing potentially lethal brain stem anaesthesia.[5-7]

It has been suggested by many authors that Atkinson's position (looking upwards and nasally)[8 9] poses an unnecessary threat to the optic nerve by placing it in close proximity to the needle path.[2-4 10] This danger was first shown radiologically by Unsöld *et al* in a cadaver with the eyes held in position by traction sutures.[11]

As it is now possible to image the excursions of the optic nerve without exposing the subject to ionising radiation,[12 13] we decided to repeat Unsöld's experiment in vivo using magnetic resonance imaging (MRI).

Methods and materials

T1-weighted inversion recovery sequences with short inversion times (STIR) (IR2000/40/150) were employed on a Picker 0·5 Tesla imager with a surface coil and two signal averages, using 5 mm slice thickness. Pilot views in three planes allowed coronal, transverse, and paraxial scanning, aligned with respect to the right optic nerve.

The normal subject was first scanned with eyes in the primary position. He was then asked to fixate in eight directions of gaze for coronal sequences, up and down for paraxial sequences, and left and right using transverse sequences.

The use of STIR imaging enables visualisation of orbital structures, with suppression of signal from the orbital fat.[14]

Results

In the primary position the ON lies within the muscle cone, a little closer to the medial rectus muscle (MR) (Fig 1E, 2). It assumes a sinuous course (Figs 3B and 4). The sinuous course of the nerve is further demonstrated in horizontal views (Fig 5B), with the nerve coming in and out of the plane of a 5 mm slice.

In upgaze, the optic nerve moved down and straightened out (Fig 1D, 2, 3A and 4). The superior rectus muscle (SR) thickened as it contracted, and the inferior rectus muscle (IR) thinned out as it relaxed (Figs 1D and 3A).

The reverse occurred on downgaze with one important difference (Figs 1F, 2, 3C, and 4): the nerve took up an S-shaped curve (Figs 3C and 4).

When looking left the nerve moved to the right. The thickening and thinning of the horizontal recti were apparent. The reverse was true with right gaze. The nerve was straightened in adduction (right nerve on left gaze and left nerve on right gaze), but adopted an S-shaped curve on abduction (Fig 5 and 6).

It can be seen in the composite traces of the paraxial and horizontal views that the anterior parts of the nerves move large distances whereas the posterior parts stay relatively still (Figs 4 and 6).

With oblique gaze, two adjacent muscles thicken and the nerve moves away from the direction of gaze (Figs 1A, C, G, I, and 2).

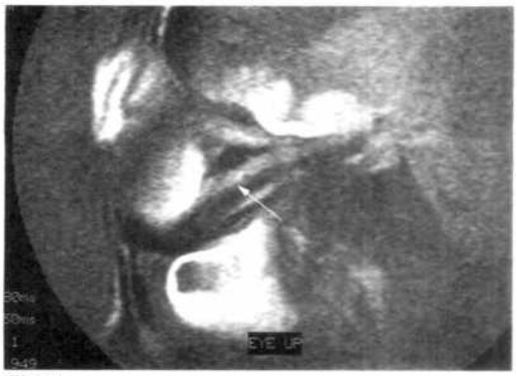

Fig 3A

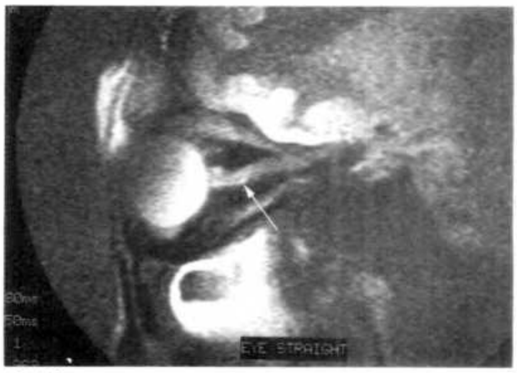

Fig 3B

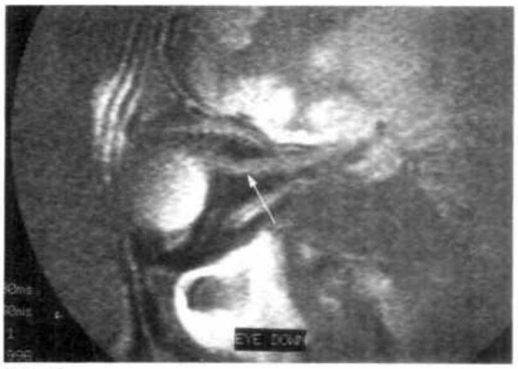

Fig 3C

Figure 3 Paraxial views of right orbit with the eye in: (A) direct upgaze. (B) primary position. (C) direct downgaze. (Arrow=optic nerve.)

Discussion

Using MRI we have been able to image the orbits

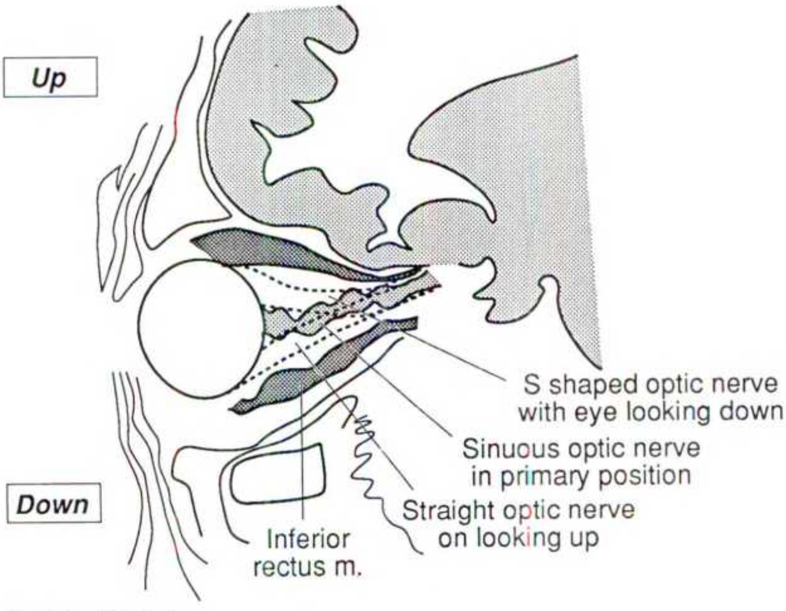
Up
Down
S shaped optic nerve with eye looking down
Sinuous optic nerve in primary position
Straight optic nerve on looking up
Inferior rectus m.

Figure 4 Composite tracing of paraxial sequences.

of a normal subject with the eyes in the nine cardinal positions of gaze. Clear differentiation of the globe, extraocular muscles, and the optic nerve was possible. We have demonstrated that the optic nerve assumes a sinuous course when the eye is in the primary position (Figs 3B, 4, 5B). This is not surprising, as the intraorbital part of the optic nerve is 25–30 mm long, and the distance it has to traverse is only 18 mm.[15] The excursion of the optic nerve with eye movement away from the direction of gaze is also expected (Table 1), though systematic imaging of the orbit with eyes in all different gaze positions had never been reported previously.

Table 1 Summary of findings

The optic nerve shifts against the direction of gaze.
The extent of the excursion of the anterior part of the optic nerve on extreme gaze is large.
There is very little movement of the posterior part of the optic nerve.
The optic nerve takes on an S-shaped curve on temporal gaze and down gaze.
On nasal gaze and on upgaze, the optic nerve becomes straight as though it were stretched.
On oblique gaze, the optic nerve shifts to opposite corner, creating a relatively large stretch of intraconal space which is nerve free.
Outside the primary position, the contracting rectus muscle thickens, with thinning of the antagonistic muscle.

Though we have only imaged one subject, we have shown that the optic nerve straightens in both adduction (Figs 5 and 6) and upgaze (Figs 3A and 4), but unexpectedly assumes an S-shaped curve on both abduction (Figs 5 and 6) and downgaze (Figs 3C and 4). This has not been described previously. An S-shaped optic nerve in abduction was also shown by Nishida *et al*, especially when the 'fixed eye' method was used.[13] There may be two reasons for the nerve adopting this shape. Firstly, the optic canal is directed forwards, slightly downwards and about 35° laterally. This inferolateral course is continued by the posterior optic nerve, which turns slightly medially.[16] In adduction, or in upgaze, the nerve moves closer to the plane of the canal, but in abduction and downgaze, the nerve is forced to bend in the reverse direction. With very little space at the apex of the orbit and with the optic nerve having a certain rigidity, it may not be possible for the nerve to turn sharply and therefore an S-shape is created. Secondly, Sevel has shown that at their origins, the SR and MR fuse with the dura mater of the optic nerve.[17] These attachments may also have some relevance in the shaping of the optic nerve in extreme gaze.

IMPLICATION FOR RETROBULBAR INJECTIONS AND SUGGESTION FOR A NEW TECHNIQUE

It is now generally believed that brain stem anaesthesia results from inadvertent injection of anaesthetic agents into the subdural space of the optic nerve.[5-7] Drysdale demonstrated this experimentally in a fresh cadaver. Migration of contrast medium along the subdural space of the optic nerve posteriorly to the chiasm, and eventually into the subdural space surrounding the pons and midbrain was shown radiologically.[18] Though the lipophilic anaesthetic agents may diffuse in a different manner from hydrophilic contrast medium, support for this mechanism comes from the recovery of anaesthetic agents in the cerebrospinal fluid following accidental brain stem anaesthesia.[19] Once the anaesthetic agent has gained access into the subdural space, it is free to diffuse to affect any part of the central nervous system.[2 10 20-23]

Historically, Atkinson suggested positioning the globe looking up and nasally for injection of anaesthetic agents into the muscle cone. His reason for recommending this position was that the inferior oblique muscle and the intermuscular septum between the IR and LR would move forward, out of the way of the needle path.[8 9] It has been suggested by many authors that the

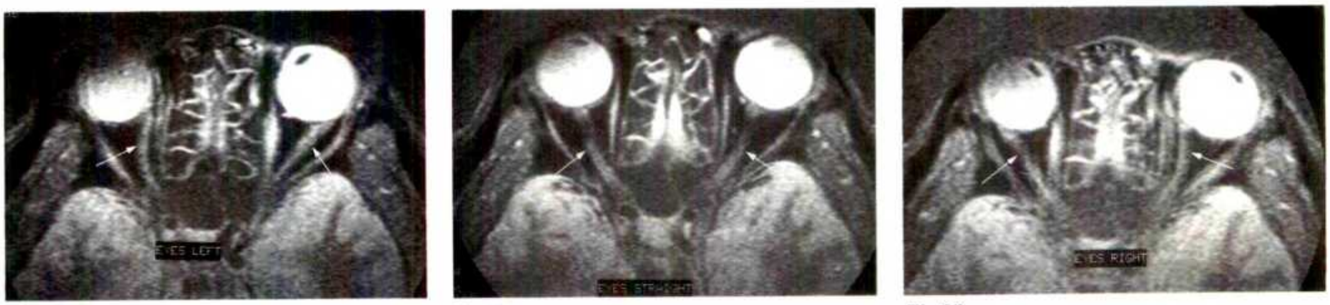

Fig 5A *Fig 5B* *Fig 5C*

Figure 5 Horizontal views of both orbits. (A) laevoversion. (B) primary position. (C) dextroversion. (Arrow=optic nerve.)

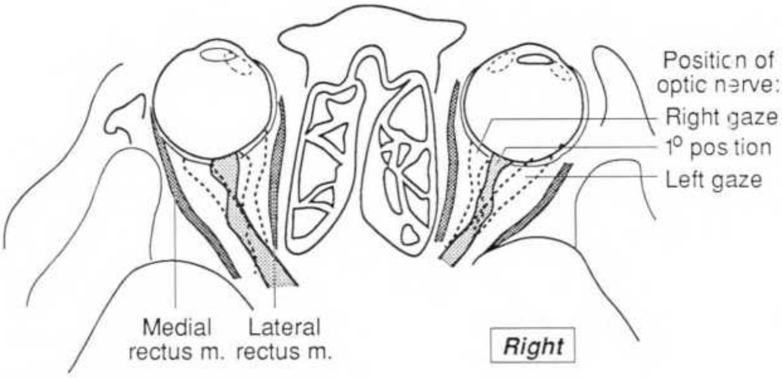

Figure 6 Composite tracing of horizontal sequences.

Atkinson's position poses an unnecessary threat to the optic nerve by placing it very close to the needle path.[2-4,10] However, it was Ünsold and her associates who first demonstrated this danger by computed tomography of a fresh cadaver. They compared the position of the optic nerve in the traditional Atkinson's position and the looking down and out postion. The two eyes were held in these positions with traction sutures. They found that the optic nerve, the ophthalmic artery and its branches, the superior ophthalmic vein, and the posterior pole of the globe were brought to close proximity of the needle. Moreover, the optic nerve and its sheath were stretched and were therefore more susceptible to puncture. They therefore recommended an alternative position with the patient looking slightly downwards and outwards.[11] In this position, the optic nerve was remote from the needle path along its entire course. This recommendation has since been endorsed by many others.[2-4,10]

We have confirmed in vivo that the optic nerve is furthest away from the needle path with the eye looking down and out (Fig 2). However, we have reservations about using this position for retrobulbar injection for two reasons. Firstly, the patient may become frightened at the sight of the needle, especially since we are extracting cataracts earlier nowadays. Furthermore, the cornea will actually get in the way (Fig 7A). These reasons limit the practicality of the down and out position, and it may be for these reasons that the very authors recommending this position also suggest the primary position as a safe alternative.[4,10]

An even safer compromise would be the down and in position (Figs 7B and 8). With the patient looking straight ahead, the surgeon places two fingers on the lateral part of the inferior orbital rim. The patient is then asked to look down and nasally at his/her own finger. The surgeon's fingers lift the globe, creating space for entry of the needle (Fig 8). A dimple is also created encouraging a posterior entry site, enabling the needle to avoid the equatorial bulge of the globe (Fig 8). As the entry site is quite posterior, the needle need only be advanced a short distance into the intraconal space. Descent of the upper eyelid is inevitable in downgaze but does not pose a real problem to retrobulbar injection (Fig 7B); after all, direct visualisation of the front of the globe in itself does not guarantee avoiding perforation of the sclera posteriorly.

Though there has been a tendency to move away from retrobulbar anaesthesia, it is still the method practised by the majority of surgeons.[2] Peribulbar injections are increasingly used but have disadvantages and are not entirely free from complications.[24-27] Other authors have gone to the trouble of using a sub-Tenon's approach into the intraconal space.[28] Curved retrobulbar needles have also been designed in an attempt to minimise the risk of complications from retrobulbar anaesthesia.[24,29-30] Others have operated successfully using a subconjunctival injection alone,[31-33] though this technique has not gained popularity, presumably because of surgeons' fear of lack of akinesia.[1]

In an editorial, Lichter pointed out that there are as many variations on the technique of retrobulbar injections as there are surgeons. Surgeons are loath to accept somebody else's technique.[34] However, there is now no doubt

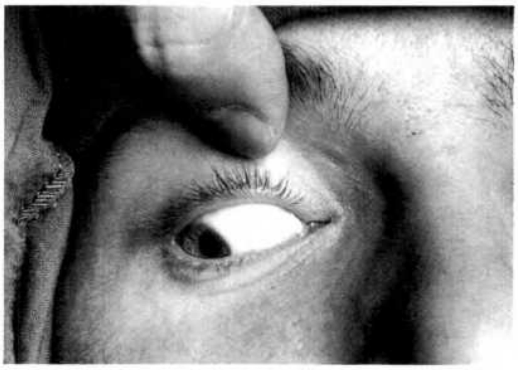

Fig 7A

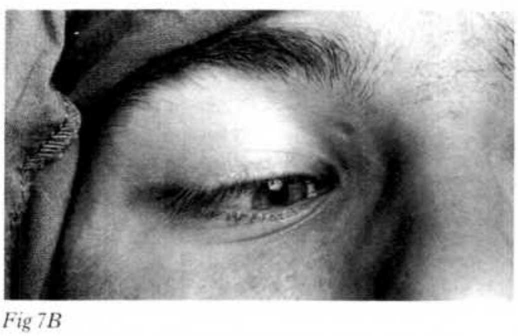

Fig 7B

Figure 7 Lid topography on downgaze. (A) Pseudo-Munson's sign prevents safe entry of retrobulbar needle. (B) The down and in position (Liu's position.).

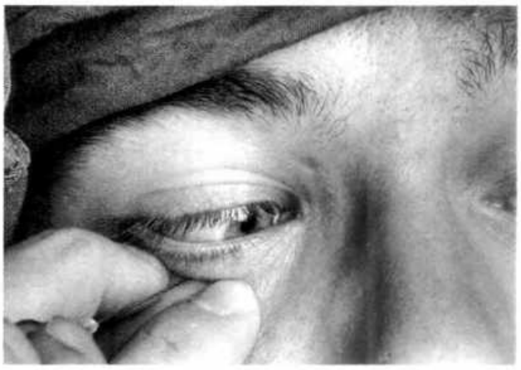

Figure 8 The globe is lifted by placing two finger tips on the lateral part of the inferior orbital margin. The dimple thus created allows a posterior entry site, enabling the needle to avoid the equatorial bulge of the globe.

that Atkinson's position is unsafe and there are medicolegal implications. It is therefore surprising to find that this position is still introduced as the standard technique.[35]

The downwards and inwards position presently advocated also moves the major orbital vessels out of the way. The risks of injecting into these vessels or causing a retrobulbar haemorrhage are therefore theoretically lower. It has been pointed out that the patient must keep the eye still while the needle is in place otherwise the bevel of the needle will act as a blade, slicing through tissues, increasing the risk of a haemorrhage.[3] The relative contraindications to local anaesthesia (long axial length, only eye, uncooperative patient, deafness, language problems, and possibly anticoagulation) still apply to this new technique.

The danger of Atkinson's position is relevant to other retrobulbar injections as well. Retrobulbar botulinum toxin A injections have been used for the treatment of acquired nystagmus to improve vision by decreasing oscillopsia (Mr J P Lee, personal communication).[36] Corticosteroids are less frequently injected into the retrobulbar space but are still occasionally used.[37] Even less used are retrobulbar alcohol injections for blind painful eyes.[37] The downwards and inwards position is also advocated for these procedures.

OTHER IMPLICATIONS

Pain on eye movement of retrobulbar neuritis

The retrobulbar pain on eye movement described by patients with optic neuritis has been thought to be caused by traction on the pain sensitive ON sheath.[16] The deformation of the ON by such movements is highlighted in vivo. Interestingly, this pain is usually maximal on abduction[38] when the ON, taking up an S-shaped curve, is perhaps most distorted. If the pain were caused by muscle traction on the sheath, adduction, with contraction of the medial rectus, would be expected to be the more painful.[16 17]

Imaging of orbital tumours

Given the clear differentiation of orbital tissue compartments using the STIR technique, improved accuracy in the analysis of the location and attachments of some orbital tumours, particularly those whose origin from the optic nerve may influence management decisions, may be possible using MRI in different positions of gaze. Based on this information, a more accurate prognosis may be given to the patient, and the most appropriate surgery planned.

Gaze evoked amaurosis

In some orbital tumours, especially cavernous haemangioma[39 40] and optic nerve sheath meningioma,[41] transient monocular loss of vision on sustained gaze in a given direction is a well recognised feature.[42 43] The large excursion of the optic nerve around such tumours may result in compromise of the haemodynamics of the ON, resulting in momentary and reversible amaurosis in certain gaze positions.[44]

Assessment of extraocular muscle thickness

A fifth application relates to thickening and thinning of the extraocular muscles when the eyes are not in the primary position. Knowledge of this effect is important when assessing muscle thickness in suspected cases of dysthyroid eye disease and orbital pseudotumours. Although the patient is usually asked to look straight ahead when the orbits are being scanned, this does not always happen. Since a number of mass lesions can also cause expansion of an extraocular muscle, imaging in different positions of gaze may assist differential diagnosis.

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Vertical transposition of the horizontal recti (Knapp procedure) for the treatment of double elevator palsy: effectiveness and long-term stability

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Abstract

Full tendon width vertical transposition (Knapp procedure) of the horizontal recti is an established treatment for double elevator palsy (DEP) but the long-term stability of the surgical results have not been well studied. We undertook a retrospective study to determine the overall effectiveness of the Knapp procedure, the postoperative stability of alignment, and the influence of prior inferior rectus muscle recession (IRc) on the magnitude of correction. Nineteen patients with DEP underwent a Knapp procedure. Eight were corrected to within 5^{Δ} of orthophoria, six were undercorrected, and five were overcorrected by at least 5^{Δ} after a mean follow-up of 3 years (to last visit or to further surgical intervention). The average vertical correction was $37{\cdot}5^{\Delta}$ in patients who underwent a prior IRc compared with $21{\cdot}1^{\Delta}$ in patients with no prior IRc ($p=<0{\cdot}0017$). Over and undercorrections were more likely to occur in patients with prior IRc. Postoperative drift was towards increased effect in all patients. The seven patients with long-term (>36 months) follow-up demonstrated an increased magnitude of correction (average$=12{\cdot}6^{\Delta}$) over an average follow-up of 76 months. The Knapp procedure had an increasing effect over time but the amount of vertical correction did not correlate with the size of the preoperative vertical deviation and was less predictable when a prior IRc had been performed.

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A monocular elevation deficiency may occur on a restrictive or paretic basis, and has an extensive differential diagnosis that includes both local, neuromuscular, and central nervous system aetiologies.[1,2] A specific type of monocular elevation deficiency characterised by underaction of both elevators of one eye (the superior rectus and inferior oblique), was first described by White[3] and was later termed 'double elevator palsy' (DEP) by Dunlap.[4] It may be congenital or acquired,[5] and is generally considered supranuclear in origin.[2,6]

Early surgical attempts to correct vertical misalignment from DEP employed either conventional vertical rectus muscle surgery[3,4] or partial vertical transpositions of the horizontal recti.[7,8] These efforts had limited success. Watson[9] reported effective treatment of DEP using a surgical technique initially developed and later described in a larger series by Knapp.[10] He described complete transposition of the horizontal recti tendons to a position adjacent to the insertion of the superior rectus (Knapp procedure). This has become a standard treatment for DEP. Only patients with free forced ductions were included in Knapp's original series; however, evidence now suggests that long-standing hypotropia from a DEP may result in secondary contracture of the inferior rectus.[6,11–14] These patients frequently demonstrate restriction on forced duction testing and require recession of the inferior rectus in addition to a Knapp procedure.

Numerous studies have reported successful treatment of DEP with a Knapp procedure,[1,6,9–11,13,15–18] yet long-term stability of alignment has not been well documented. In this study, we analysed the long-term alignment, and the effect of prior inferior rectus recession (IRc) on the magnitude of the vertical correction following a Knapp procedure.

Subjects and methods

A computer data base retrieval system at the University of Iowa Pediatric Ophthalmology and Strabismus service was searched for all patients with congenital or acquired DEP who underwent a Knapp procedure between 1966 and 1990. A retrospective chart review was performed on all 21 patients. All had other causes for monocular limitation of elevation excluded; including thyroid eye disease, a history of orbital trauma, third nerve palsy, a past history of orbital inflammation, orbital tumour, or surgical recession or disinsertion of the superior rectus muscle.

All patients had pre and postoperative evaluations performed at the University of Iowa which included assessment of visual acuity, pupillary function, motility, slit-lamp, and ophthalmic examination. Fusional status was assessed using the Worth 4-dot test at distance and near, and using the Titmus stereoacuity test. Pre and postoperative motility measurements were obtained by prism cover testing while fixating in primary gaze at an accommodative target 6 metres away. Neutralising prisms were held in front of the eye with the DEP to measure the primary deviation. All patients had supraplacement of the medial and lateral recti to a position within 2 mm of the position described by Knapp (Fig 1).[10] Short-term measurements were obtained 1 week postoperatively and the last measurements were those of the most recent clinic visit or the examination preceding any subsequent rectus muscle surgery.

Two patients were excluded from this study. The first patient had severe restriction noted at the time of Knapp surgery but no release of the

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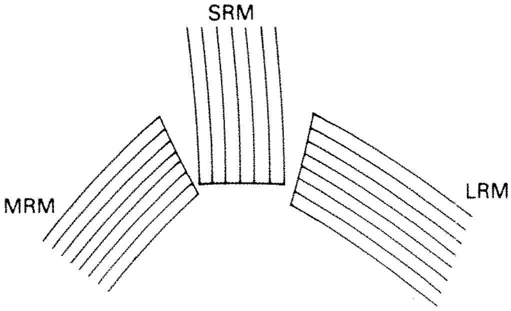

Figure 1 Knapp procedure. Illustration of the transposed tendon site for the medial rectus muscle (MRM) and the lateral rectus muscle (LRM). (SRM – superior rectus muscle) of the left eye.

Table 2 Effect of prior inferior rectus recession on the vertical correction from the Knapp procedure

	Amount corrected *No prior IRc*	*Prior IRc*
n	13	6
Mean correction (△)	21·1	37·5
Standard error (△)	2·6	3·0
High (△)	39·0	46·0
Low (△)	5·0	27·0

Unpaired *t* test between both groups:
Degrees of freedom = 17; t = 3·72; p = 0·017

restriction was performed; consequently, no correction in primary position was noted postoperatively. The second patient had a superior rectus recession performed in the contralateral eye at the time of the Knapp procedure and was also noted to develop a dissociated vertical deviation in the eye with the DEP. This patient was excluded because concomitant vertical rectus surgery at the time of the Knapp procedure prevented accurate assessment of the magnitude of correction attributable to the transposition.

Results

Nineteen patients underwent a Knapp procedure, and were aged between 1 and 35 years at the time of surgery (mean 7·6 years). Seven patients had a history of prior extraocular muscle surgery. One patient had a superior rectus resection and medial rectus resection before the Knapp procedure. Six patients had a prior IRc in the eye that 3 to 6 months later underwent a Knapp procedure.

Prior to their Knapp procedure 17 patients had a manifest vertical deviation ($\geq 5^{\Delta}$) in primary gaze. The largest deviation was 55^{Δ} and the average deviation for all patients was $28{\cdot}2^{\Delta}$. The preoperative deviation measured immediately before the Knapp procedure averaged $30{\cdot}5^{\Delta}$ for the six patients who underwent a prior IRc and $22{\cdot}8^{\Delta}$ in the 13 patients who did not. The other two patients had a latent vertical deviation in primary gaze and a hypotropia on elevation. Eleven patients preferred fixation with the unaffected eye and two patients alternated fixation. Five patients had evidence of preoperative fusion but required an abnormal head position to maintain fusion.

The follow-up for our 19 patients ranged from 6 to 144 months (mean 36·2 months). Seven patients had postoperative follow-up greater than 36 months, and their average follow-up was 76 months (Table 1) (only one of these had a prior IRc). When the vertical deviation in primary position 1 week postoperatively was compared with that of the most recent follow-up visit all seven patients demonstrated an increased magnitude of vertical correction with time (average $12{\cdot}6^{\Delta}$, range 5^{Δ}–26^{Δ}). A one sample t test comparing the observed change 1 week postoperatively with that of the more recent visit, with a null hypothesis of no change, generated a t value of 4.30 (p = 0·0051) for a two-tailed distribution with 6 degrees of freedom. Postoperative drift was invariably towards increased effect from the surgery with time, but no consistent trend with regard to its timing was noted. Some patients drifted within the first few postoperative weeks; others up to several years later.

Table 1 Stability of alignment following the Knapp procedure for patients with ≥36 months follow-up

Case	*Pre-op deviation (△)*	*Short-term post-op deviation (△)*	*Duration of follow-up (months)*	*Long-term post-op deviation (△)*	*Amount post-op drift (△)*
1	35 LHT	14 LHT	144	4 RHT	18
2*	18 LHT	2 RHT	96	28 RHT	26
3	20 LHT	20 LHT	84	5 LHT	15
4	20 LHT	4 RHT	36	10 RHT	6
5	30 RHT	2 RHT	60	3 LHT	5
6	20 LHT	2 LHT	55	4 RHT	6
7	25 LHT	12 LHT	57	Ortho	12
Mean			76		12·6
Standard error					2·9

t test comparing drift values with null hypothesis of no drift
Degrees of freedom = 6; t = 4.30; p = 0·0051

* Prior inferior rectus recession

Table 2 shows the magnitude of vertical correction observed in the 19 patients who underwent a Knapp procedure. An unpaired t test comparing the magnitude of correction achieved in the group of patients who underwent a prior IRc generates a t value of 3.72 (p = 0·0017 with 17 degrees of freedom).

Vertical alignment following the Knapp procedure is shown in Table 3. The success of vertical alignment was lower in patients who underwent a prior IRc in comparison to patients who did not. Eight patients were successfully corrected to within 5^{Δ} of orthophoria, six were undercorrected and five were overcorrected by at least 5^{Δ} at the last follow-up visit. Overcorrection occurred in 50% (3/6) of patients who underwent prior IRc and only in 15% (2/13) of the patients who had no prior IRc. The frequency of undercorrection was also higher in the patients who underwent prior IRc. Regression analysis revealed that the magnitude of vertical correction obtained by the Knapp procedure was not to the magnitude of preoperative deviation regardless of whether or not a prior IRc had been performed.

Table 3 Success of vertical alignment following Knapp procedure

	Prior inferior rectus recession	*No prior inferior rectus recession*
Number of patients undercorrected $\geq 5^{\Delta}$ of orthophoria	2	3
Number of patients corrected to within 5^{Δ} of orthophoria	1	8
Number of patients overcorrected $\geq 5^{\Delta}$ of orthophoria	3	2
Total number of patients	6	13

A significant (≥10△) horizontal deviation was present in 11 patients at the time of their Knapp surgery (six patients were esotropic and five were exotropic). Five patients had horizontal rectus muscle surgery performed at the time of their Knapp operation. The horizontal surgery was performed in the same eye as the Knapp procedure in three cases, and in the contralateral eye in two cases. All three patients who had horizontal surgery in the same eye as the Knapp procedure achieved a postoperative horizontal alignment within 10△ of orthophoria. Both patients who had concomitant horizontal rectus surgery in the contralateral eye had a postoperative horizontal deviation of 20△ (one patient was undercorrected and one patient was overcorrected).

Information on postoperative fusional status was available for 16 patients and fusion was observed in seven patients. Five of these seven patients demonstrated evidence of fusion preoperatively. Two patients with postoperative fusion had long-term follow-up (>36 months). The postoperative vertical drift for both of these patients was 5△ and 6△ respectively, and represented the two lowest drift magnitudes of the seven patients for whom long-term follow-up was available.

Discussion

The optimal surgical treatment for double elevator palsy remains controversial. Successful alignment has been achieved following partial tendon vertical transposition of the horizontal recti,[7] conventional vertical rectus, and oblique surgery,[4] the Callahan (modified Jensen) procedure,[14] and both partial,[8 16 18] and full[1 6 9 10 15 16] vertical tendon width transpositions of the horizontal recti. The largest series of patients undergoing surgery for DEP was reported by Dunlap[4] in 1952. Eighteen of 39 patients achieved a 'good or excellent' result, though categorisation of results was arbitrary. None of these patients were treated with the full-muscle transposition procedure subsequently popularised by Knapp.[10]

Thirteen to 73% of patients with DEP may develop secondary contracture of the inferior rectus in the paretic eye.[6 11 15 17] Restriction can be detected by comparison of duction with version movements, forced duction testing,[1 10] and vertical saccadic velocity studies.[11 12] If restriction is present it must be relieved by recession of the inferior rectus in order for a Knapp procedure to be successful.[6 13 16 17] In some cases, the vertical deviation in primary gaze may be satisfactorily corrected by IRc alone.[6] Simultaneous IRc and vertical transposition of both horizontal recti entails disruption of five of the anterior ciliary arteries – increasing the risk for postoperative anterior segment ischaemia.[14] Consequently, a two-step approach, consisting of IRc followed by a Knapp procedure, has been advocated for the correction of vertical deviation in patients with evidence of restriction.[6]

Table 4 compares the average magnitude of vertical correction from the Knapp procedure observed in this study with that of nine previous reports. Our study represents the largest series of patients undergoing the Knapp procedure for the correction of DEP. The average magnitudes of correction in primary gaze in previous studies are similar to those found in this study. We found a statistically significant difference ($p<0.0017$) in the magnitude of vertical correction in patients with an IRc performed prior to Knapp surgery (38△) compared with those with no prior IRc (21△). Lee[17] has reported equivalent magnitudes of vertical correction in patients undergoing a Knapp procedure with a simultaneous IRc. Knapp[10] simultaneously recessed the inferior rectus in two patients without preoperative restriction, and postoperatively both patients obtained significant overcorrections in primary gaze. This suggests that prior IRc reduces the infraducting force of the inferior rectus, permitting a greater elevating effect from the superiorly transposed horizontal recti.

Patients who underwent a prior IRc were less likely to achieve successful vertical alignment than patients who did not undergo a prior IRc (Table 3). Patients having a prior IRc also had a greater magnitude of vertical change, though overcorrection was not significantly more frequent than undercorrection. This may be attributable to their larger magnitudes of preoperative vertical deviation.

Some authors advocate grading the magnitude of vertical displacement of the horizontal recti on the basis of the magnitude of the vertical deviation in primary gaze.[16 18] Graded transpositions were not included in this study. In this study the amount of vertical correction in primary gaze obtained by the full Knapp procedure was independent of the size of the preoperative deviation and was not fully predictable for any given patient. However, the data in Figure 2 suggest that a partial tendon transposition could be considered if a patient has had a prior IRc and has less than 25△ vertical deviation in primary gaze, or if the patient has not had a prior IRc, and the deviation in primary gaze is less than 10△.

The longitudinal data reported in this study suggest that the magnitude of vertical correction following a Knapp procedure increases with time. By comparison, Knapp,[10] in his original series did not quantitate postoperative drift, however, he did note 'no deterioration in result' with an average follow-up of 4·5 years. The retrospective nature of our study limits the

Table 4 Correction of vertical deviation by Knapp procedure

Author	*Number of patients with DEP*	*Average vertical deviation corrected in primary gaze (△)*	*Comments*
Watson[9]	2	30	
Knapp[10]	15	38	All had negative preoperative forced ductions. Nine patients had primary DEP
Harley[13]	4	25–40	One patient with positive forced ductions excluded
Cooper[1]	6	25	1/6 had simultaneous horizontal surgery
Scott[6]	5*	37	Prior IRc, no restriction at the time of the Knapp
Barsoum-Homsy[16]	2	29	Full Knapp
Lee[17]	11	19	Knapp only
		23	Knapp+simultaneous IRc
Flicker[15]	15	?	Pre and post-op deviations not given
Present study	19	21	Knapp only
		38	Prior IRc followed by Knapp
Dunlap[18]	2	35	Patients graded supraplacement ≥10 mm

*These patients are included in the present study

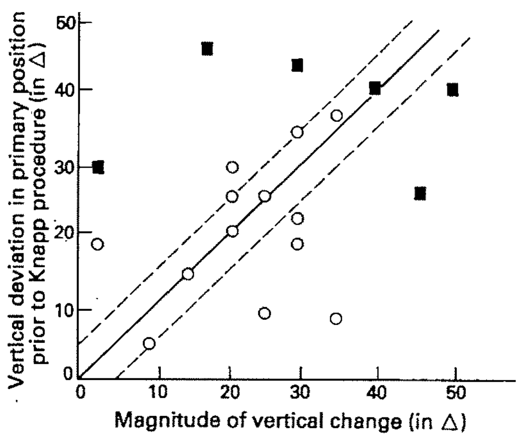

Figure 2 Relationship of preoperative deviation to magnitude of change obtained by the Knapp procedure for each patient (45° line [solid] indicates exact correction of the deviation; broken lines indicate=/-5^{Δ} of desired correction. ○/■ =No prior/prior inferior rectus recession.

number and timing of intermediate follow-up visits available for analysis. However, the available data indicated that significant drift can occur at any time from 1 week to several years following surgery, and that the timing of this drift was variable. Regardless of which postoperative measurements were compared, all patients consistently drifted towards increased elevation over time. This has important clinical implications, as in the immediate postoperative period undercorrected patients can expect some drift toward an improved alignment, while overcorrected patients can expect to worsen.

The goal of most strabismus surgeries is to achieve postoperative fusion. Seven patients in this study had evidence of fusion following the Knapp procedure and five of these had preoperative fusion. All five had excellent alignment and no abnormal head position postoperatively. Fusion was first detected following Knapp surgery in the two other patients. Either these patients had gaze-dependent fusion preoperatively that was unrecognised because fusional testing was performed in only one position of gaze, or satisfactory postoperative alignment afforded these patients the opportunity to develop fusion. Achieving postoperative fusion may confer improved long-term stability of alignment. While only two patients with postoperative fusion had long-term follow-up, they drifted less than the other five patients for whom long-term follow-up was available.

In summary, the Knapp procedure can effectively improve or correct the hypotropia in patients with DEP and have an increased effect over time. The magnitude of correction is greater if a prior inferior rectus recession is performed, and is independent of the preoperative deviation.

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A method for assessing the accuracy of surgical technique in the correction of astigmatism

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Abstract

Surgical results can be assessed as a function of what was aimed for, what was done, and what was achieved. One of the aims of refractive surgery is to reduce astigmatism; the smaller the postoperative astigmatism the better the result. Determination of what was done – that is, the surgical effect, can be calculated from the preoperative and postoperative astigmatism. A simplified formulation is described which facilitates the calculation (magnitude and direction) of this surgical effect. In addition, an expression for surgical accuracy is described, as a function of what was aimed for and what was achieved.

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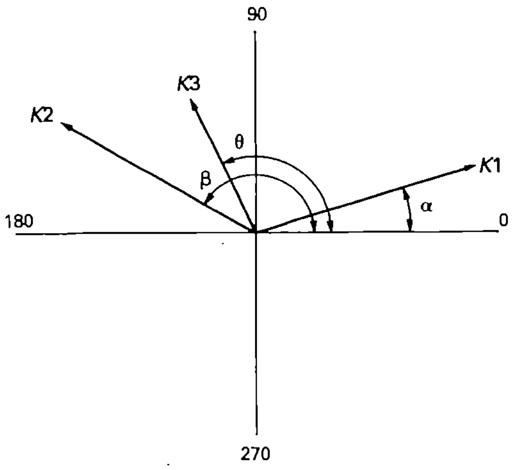


Figure 2 Representation of preoperative astigmatism, K1 *at angle* α, *postoperative astigmatism,* K3 *at angle* θ, *due to the surgical effect,* K2 *at angle* β.

Modern methods of assessing corneal topography have greatly improved the understanding of the changes in corneal curvature which may be induced by surgery. Keratometry, refraction, or computerised corneal topography can be used to measure preoperative ($K1$) and postoperative ($K3$) astigmatism. A mathematical calculation is required merely however to determine the astigmatism induced by the surgery ($K2$) – that is, the difference between $K1$ and $K3$.[1] It is accepted that it is inadequate to judge surgical effect ($K2$) by merely subtracting $K3$ from $K1$ without taking the meridions of $K1$ and $K3$ into account.[1]

The first part of this communication describes a formula to facilitate the calculation of $K2$, the measurement of which is necessary to evaluate and audit surgical technique, especially in refractive surgery. The second provides a simple function to assess the accuracy of the surgical technique.

Consider the following example: a patient's preoperative refraction is plano/+5·00 at 180° and postoperatively is +4/+1·00 at 180°. The surgical effect ($K2$) therefore, was to flatten the horizontal meridian by 4 dioptres – that is, to induce a +4·00 dioptre cylinder at 90°. When $K1$ and $K3$ do not lie in the same axis or are not at 90° to one another, then the calculation of $K2$ becomes more complex.[1]

In 1975 Jaffe and Clayman[1] adapted an older method,[2–4] to calculate $K2$ in cataract surgery. In essence the power of a cylinder (F) at an angle (θ) to its principal meridian, is described by the relationship $F\cdot\text{cosine}^2\theta$ (Fig 1). Using this relationship they showed that the magnitude and direction (β) of $K2$ can be calculated from $K1$ and $K3$ by using the law of cosines[1] (Fig 2 and equations 1 and 2 in Appendix).

This derivation, however, does not readily determine in which quadrant $K2$ lies – that is, 0° to 90° or 90° to 180°. If $K1$ is +1·50 dioptres at 25° and $K3$ is +3·00 dioptres at 100° (Fig 3), then from equation 1, $K2$ is plus or minus 4·36

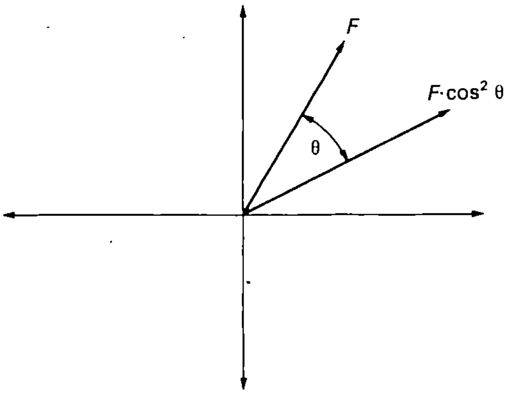


Figure 1 The power of a cylinder (F) *at an angle* (θ) *to its principal meridian is described by the relationship* F·*cosine*²θ.

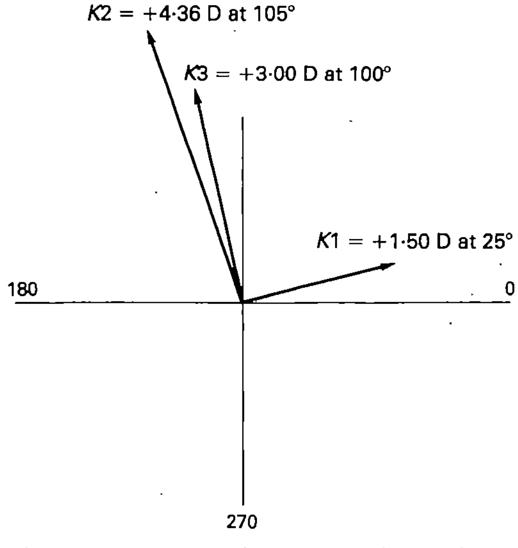
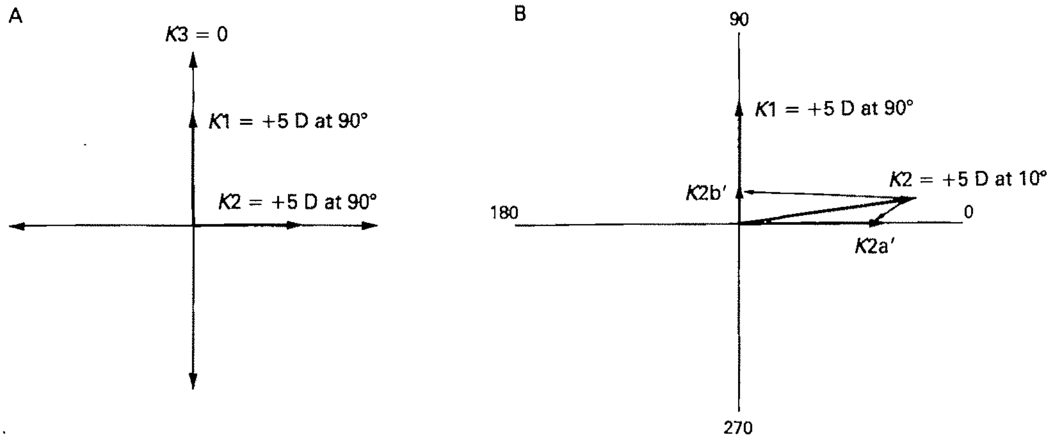


Figure 3 Representation of K2. K1 *is +1·50 D at 25°* (α), K3 *is +3·00 D at 100°* (θ), *and* K2 *is +4·36 D and lies in the second quadrant at 104·96°* (β).

Figure 4 (A) $K1$ is +5·00 D at 90°. $K2$ is of equal magnitude to $K1$ (that is +5·00 D) and placed along the desired surgical meridian (90° to $K1$) at 0°, so that $K3=0$. (B) The effectiveness of $K2$, that is, $K2'$. $K1$ is +5·00 D at 90° and $K2$ is +5·00 D at 10° (that is, 80° to $K1$, or 10° away from the desired meridian) resulting in a residual astigmatism of $K3=+1{\cdot}74$ D. $K2'$ is the net effect of $K2$ at 90° to $K1$ – that is, $K2a'-K2b'$.



dioptres so that β is 14·96° or −14·96° (345·04°). As shown in Figure 3 however, $K2$ lies in the second quadrant, therefore β is 14·96°+90°= 104·96°.

An alternative method for the calculation of $K2$ and its location

This communication provides an alternative method enabling the direct calculation of β and $K2$. Consider Figure 2, with $K1$ at angle α and $K2$ at angle β, resulting in $K3$ at angle θ. It can then be shown that:

$$K2=K3\cdot\cos 2(\beta-\theta)-K1\cdot\cos 2(\beta-\alpha)$$

(Appendix, equation 3)

with β calculated directly from equation 4 (see Appendix). If $K2$ is negative (a minus cylinder), conversion to a positive cylinder can be made by adding 90° to β if β is greater than 0, or subtracting 90° from β, if it is less than 0° (see Appendix).

Given the example above (Fig 3), where $K1$ is 1·5 D at 25° and $K3$, 3 D at 100°, then using equations 3 and 4, $K2$ is −4·36 D at 14·96°. If preferred, $K2$ can then be converted to a positive cylinder – that is, +4·36 D at 104·96° by adding 90° to β.

Assessing the accuracy of refractive surgery

Methods currently in use to further assess the effects of surgery[5] are:

1. The vector of flattening ($\mathbf{V_F}$) – that is, the steepest preoperative meridian minus the steepest postoperative meridian.
2. The vector of steepening ($\mathbf{V_S}$) – that is, the postoperative flat meridian corresponding to the preoperative flat meridian minus the preoperative flat meridian.
3. The flat/steep ratio – that is, $\mathbf{V_F/V_S}$.
4. The average change in spherical equivalents – that is, average postoperative measurements minus average preoperative measurements.

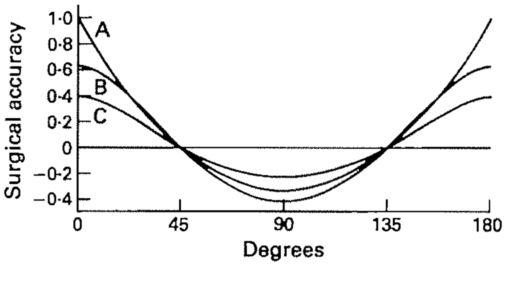


Figure 5 Surgical accuracy (SA) as defined by the function $K2'/K2+K3$. Graph depicting SA for three values of $K2$, as $K2$ is rotated away from its optimum meridian. (A) $K2=K1$, (B) $K2=7/5K1$, and (C) $K2=2/5K1$.

Collectively the size and direction of $K1$ and $K3$, the surgical effect, $K2$, and the overall change in spherical equivalent, give a measure of surgical achievement. It is more difficult however, to provide a single measure which reflects surgical accuracy. $K3$ by itself provides one measure – that is, the nearer $K3$ is to zero, the better the surgical achievement. It does not reflect the magnitude of the surgical success (or failure), nor does it indicate whether the surgery was in the desired meridian. Furthermore, the ratio of the pre- and postoperative astigmatism – that is, $K3/K1$ does not distinguish, for example, between no effect – that is $K3=K1$, or twice the required effect, such that $K3$ still equals $K1$. Likewise, the departure from the desired surgical meridian is not indicated.

The ideal surgical meridian of $K2$ is at 90° to $K1$ ($K1$ and $K2$ both deemed positive or negative). Consider the following example, where $K1$ is +5 D at 90° (see Fig 4A). In order to correct this amount of astigmatism, a surgical cylinder of equal magnitude to $K1$ would need to be placed at 90° to $K1$. That is, $K2=+5$ D at 0° (or $K2=-5$ D at 90°). This would then result in no postoperative astigmatism, that is $K3=0$ (see Fig 4A).

If $K2'$ represents the net effect of $K2$ in the desired surgical meridian (90° to $K1$) (Appendix equation 5 and Fig 4B), then the ratio $K2'/K2+K3$ provides a reasonable surgical accuracy (SA). In the above example, $K2'$ equals $K2$ (Appendix, equation 5) so that surgical accuracy is:

$$\mathrm{SA}=+5{\cdot}0/(+5{\cdot}0+0{\cdot}0)=+1$$

If, however, surgery resulted in $K2$ of +5 D being placed at 10° (is 80° to $K1$, Fig 4B), then the effectiveness of $K2$ at 0° – that is $K2'$, in reducing $K1$ is +4·67 D in the desired meridian, or 0·33 D less than the ideal (Appendix, equation 5). The resulting postoperative astigmatism is +1·74 D and SA is 4·67/(5+1·74)=0·69 (Figs 4B and 5).

If $K2$ is placed nearer the meridian of $K1$ than the desired meridian, then $K2'$ and therefore SA, are less than 0. This ratio for SA lies between −0·5 and +1 and reflects the magnitude of over- or undercorrection. A negative value also indicates a departure of more than 45° from the optimum meridian for $K2$. A result of +1 indicates that both the magnitude and the meridian of $K2$ were optimal. A single measure is thus provided with which to determine surgical accuracy. Figure 5 is a graph showing the effect on SA as the meridian of $K2$ is rotated through 180° for three different values of $K2$.

The equations for $K2$, b, b transposed, $K2'$, and surgical accuracy have been written for use on a Lotus compatible spreadsheet and are given in the Appendix.

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Appendix

CALCULATION OF $K2$ AND b

$$K2^2=K1^2+K3^2-2.K1.K3.\cos 2(\theta-\alpha) \tag{1}$$

$K1$ is the preoperative astigmatism at angle α,
$K3$ is the postoperative astigmatism at angle θ,
$K2$ is the surgically induced astigmatism or surgical effect at angle β, where

$$\sin 2\beta=(K3.\sin 2\theta-K1.\sin 2\alpha)/K2 \tag{2}$$

From Figure 2,

$$\begin{aligned}K2&=(K3\cos^2(\beta-\theta)-K1\cos^2(\beta-\alpha)-K3\sin^2(\beta-\theta)+K1\sin^2(\beta-\alpha))\\&=K3\cos 2(\beta-\theta)-K1\cos 2(\beta-\alpha)\end{aligned} \tag{3}$$

where

$$2\beta=\arctan\{(K1\sin 2\alpha-K3\sin 2\theta)/(K1\cos 2\alpha-K3\cos 2\theta)\} \tag{4}$$

If $K2$ is negative, conversion to a positive cylinder can be made as stated in the text, by adding or subtracting 90° to or from β, if β is greater than or less than 0° respectively. This can be verified by taking the second differential of $K2$ with respect to β – that is,

$$\begin{aligned}d^2K2/d\beta^2&=-4K3\cos 2(\beta-\theta)+4K1\cos 2(\beta-\theta)\\&=-4K2\end{aligned}$$

Therefore, if $K2$ is negative, $d^2K2/d\beta^2$ is >0 and $K2$ is a minimum for that value of β. Adding or subtracting 90° from β, will make $K2$ positive and a maximum, as $d^2K2/db^2<0$.

SURGICAL ACCURACY

From Figure 4B, the effectiveness of $K2$ – that is, $K2'$, is $K2'=K2a'-K2b'$

$$\begin{aligned}K2'&=K2\cos^2(\beta-(\alpha+90))-K2\cos^2(\beta-\alpha)\\&=K2[\sin^2(\beta-\alpha)-\cos^2(\beta-\alpha)]\\&=-K2\cos 2(\beta-\alpha)\end{aligned} \tag{5}$$

Surgical accuracy (SA), can be defined as

$$SA=K2'/(K2+K3) \tag{6}$$

FOR USE IN A SPREADSHEET

The following equations, when entered into the appropriate columns of a Lotus compatible spreadsheet, can be used to calculate surgical effect ($K2$), its angle β and the surgical accuracy.

```
K2=K3*@Cos(@PI/90*(β–θ))–K1*@Cos(@PI/90*(β–α))

β=90/@PI*@Atan(((K1*@Sin((@PI/90)*α))–
   (K3*@Sin((@PI/90)*θ)))/((K1*@Cos((@PI/90)*α))–
   (K3*@Cos((@PI/90)*θ))))

β converted*=@IF(K2<0#AND#β<0#AND#b>–90,β+90,
            (@IF(K2<0#AND#β<0#AND
              β<–90,β+270,
            (@IF(K'<0#AND#β>0,β+90,(@IF
            (K2>0#AND#β<0,β+180,β)))))))
```

*this allows $K2$ to be used as a positive cylinder and expresses b as an angle between 0° and 180°.

```
K2'=K2*((@Sin((PI/90)*(β–α)))^2–
        (@Cos((PI/90)*(β–α)))^2)
Surgical accuracy=K2'/(K2+K3)
```

British Journal of Ophthalmology 1992; 76: 741–742

Localisation of corneal foreign bodies

L G Kaye-Wilson

Abstract

Of 50 patients attending the eye casualty department with a corneal foreign body (FB), 41 were able to say where they felt the FB and 78% of these were localised correctly for side or level of cornea. Patient handedness did not influence FB location. Indicating the upper lid was a particularly poor guide to localisation, whereas FB sensations within the palpebral fissure, in the lower lid or medially or laterally were good guides to actual FB location. A simple method of recording FB location by zone and clock hour is proposed.

(*Br J Ophthalmol* 1992; 76: 741–742)

Corneal foreign body (FB) removal constitutes a significant proportion of the workload of both general and ophthalmic casualty departments. General practitioners, industrial nurses, and general casualty officers are involved in corneal FB management. It would be useful if some means of directing their search for the location of a corneal FB existed, especially if a slit-lamp is not available.

Pain from a corneal FB is usually projected to the eyelid. The accuracy of this pain projection as a method of self-localisation of corneal FBs was investigated by developing a simple system to record corneal FB position and comparing this with the patient's self-localisation.

Methods

Fifty consecutive patients with metallic corneal FBs (and no previous ocular disease) were seen in the ophthalmic casualty department. A note was made of the mode of injury, the patient's occupation, which eye was injured, whether the patient was right or left-handed, and how the FB was removed. Localisation was assessed by asking the patient to point to where he felt the discomfort (with the eye open). This was recorded as a vertical (1–5) and horizontal (A-E) localisation score as shown in Figure 1. After slit-lamp examination, FB location was recorded by zone and clock hour (Fig 2), using an abbreviated code. For example, R II/3^{30} denotes the paracentral third of cornea at the half-past-three position in the right eye. FBs were removed under local anaesthesia by cotton bud, 21-gauge needle or, if more adherent or deeper, with a burr.[1,2]

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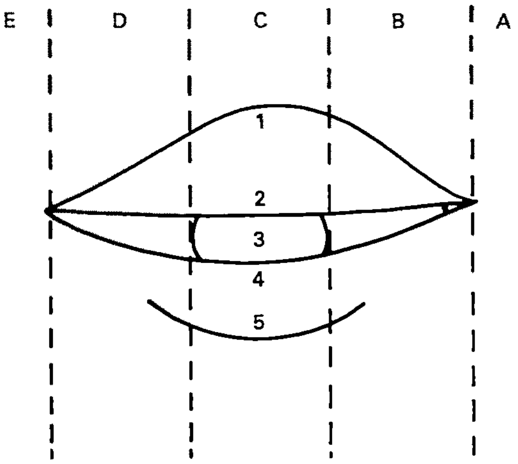

Figure 1 Patient self-localisation coding. Schematic right eye (the left is a mirror image). Score A-E=horizontal; score 1–5=vertical.

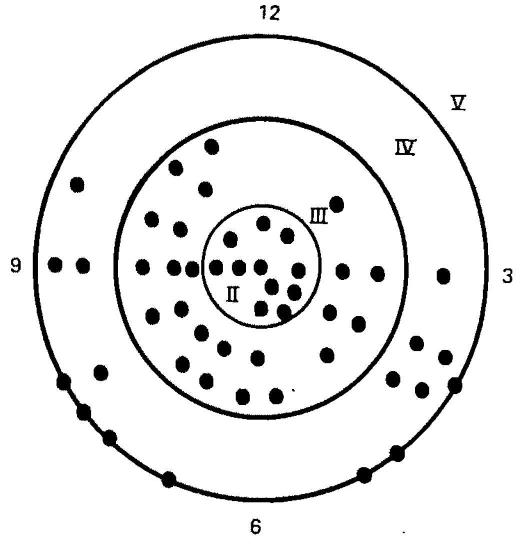

Figure 2 Corneal location coding: zone I central point, zone II paracentral third, zone III mid third, zone IV peripheral third, zone V limbal. Fifty corneal FB locations are shown.

Results and analysis

Ninety four percent of patients in this study (47/50) were male; 72% (36/50) of FBs were work-related. Of these patients, 89% (32/36) had not been wearing any eye protection at the time of injury. Twenty eight of 50 FBs could be removed by needle alone; 20/50 required burr removal; only 2/50 were removed by swab alone. There was no significant difference in frequency of needle versus burr FB removal between any of the groups described below.

ACCURACY OF LOCALISATION

All 50 FB locations are summarised in Figure 2, by zone and the nearest clock hour. Actual FB locations were compared with localisations (where the patients believed the FBs were situated by their sensation of pain). For example, if the FB was located in the upper half of the cornea, vertical localisation was correct if the patient felt the FB in the upper lid (score 1–2 in Fig 1). Similarly, if the FB was located in the medial half of the cornea, horizontal localisation was correct if the patient felt the FB medially (score A–B in Fig 1).

Nine patients found FB localisation impossible, including three who did not feel the FB. Of the remaining 41 patients who believed they could localise the FB sensation, 14 localised correctly to both side and level, whilst 18/41 localised correctly to side only or level only – that is, 32/41 (78%) localised side and/or level correctly. Only 9/41 patients localised incorrectly in both directions and of these, 89% (8/9) were misleadingly felt in the upper lid.

Twenty three patients indicated that they felt the FB in the upper lid (score 1–2): however, only 7/23 (30%) actually had an FB in the upper half of the cornea. On the other hand, nine patients felt the FB in the lower lid (score 4–5), and seven of these (78%) did have an FB present in the lower half of the cornea. Similarly, nine patients said that they felt the FB within the palpebral aperture (score 3); seven of these (78%) had an FB on the central horizontal line from 9 o'clock to 3 o'clock, with the other two being just below the line.

Thirty one patients felt pain from the FB either nasally or temporally (score A, B, D, E); 74% (23/31) were localised correctly with respect to the 12 o'clock to 6 o'clock vertical line, with equal accuracy nasally and temporally.

EFFECT OF HANDEDNESS

To assess whether patient handedness influenced the position of the FB on the cornea, patients were grouped into those with an FB in the eye of the dominant side (22/50) and those with an FB in the eye of the non-dominant side (28/50).

Patients were also divided into those with an FB on the right half or the left half of the cornea, regardless of which eye the FB had landed on. Each cornea was divided into right and left sides by a vertical line from 12 o'clock to 6 o'clock. Seven FBs were recorded on this line. Excluding these, 19 out of 43 landed on the dominant side of the cornea.

Discussion

As a result of this study it appears likely that handedness does not influence FB location. Percival described a trend towards injury of the eye of the non-dominant side in his study of intraocular FBs.[3] However, non-use of eye protection is of very much greater significance.[4]

Most of the FBs landed on cornea within the palpebral aperture as the eyelids protect the remaining cornea. However, without the aid of a slit-lamp, it is often difficult to locate corneal FBs. This study suggests that FBs felt under the upper lid are unlikely to be in the upper half of the cornea, whereas FBs felt in the lower lid are likely to be in the lower half of the cornea. Similarly, if discomfort from an FB is felt within the palpebral aperture and not on the lid margins, the FB is very likely to be on the central band of cornea. Also, nasal or temporal localisation correlates well with actual location.

No universal system of recording corneal FB location is in use. Precise records are clearly of medicolegal importance: for example, multiple corneal scars may be present in a case for an industrial compensation claim, but which scar is relevant to the claim?

There are many alternatives to the system of recording FB location used in this study. Drawing a dot inside a circle to represent a corneal FB is inaccurate. Verbal records are often vague – 'central' may in fact be paracentral. Slit-lamp measuring grids and messy 'grid' rubber stamps for the case notes are an added expense. In contrast, the clock hour scheme is easily understood and accurate (although zones are more easily remembered by name than number).

This study has shown a useful clinical application for corneal sensitivity mapping.[5] It is also hoped that the system of recording corneal FB location might be introduced into general use.

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British Journal of Ophthalmology 1992; 76: 743–745

MINI REVIEW

Von Hippel-Lindau disease

Von Hippel-Lindau (VHL) disease is a dominantly inherited familial cancer syndrome with variable expression. The most frequent complications are retinal angiomatosis, cerebellar and spinal haemangioblastomas, and renal cell carcinoma.[1] Renal, pancreatic, and epididymal cysts are also common. Phaeochromocytoma occurs in less than 10% of patients, but in some families this is the most frequent complication. Although VHL disease has been considered to be rare, it is frequently underdiagnosed, and a recent study in East Anglia has demonstrated a minimum birth incidence of 1 in 36 000.[2] Furthermore, for each affected individual there are likely to be another four or five relatives at significant risk (25% or more) of becoming affected so that the management of families with VHL disease is a common problem.[3]

The penetrance of VHL disease is age and tumour dependent. Most patients present in the second and third decades, but onset may be in infancy or in old age.[1,4] Retinal angiomatosis is the most frequent initial complication of VHL disease and the ophthalmologist has a central role in the diagnosis and management of patients with this disorder. The proportion of patients with retinal angiomatosis who have VHL disease is not well defined (estimates vary between 25% and 80%), but all patients, and their first degree relatives, with solitary retinal angioma should be investigated for evidence of VHL disease. The mean age at diagnosis of retinal angioma in VHL disease is 25 years and the younger the age at onset the more likely is VHL disease. Among patients with retinal angioma the presence of multiple retinal angiomas is diagnostic of VHL disease, as is a single retinal angioma and a positive family history or another manifestation of the disorder (such as cerebellar haemangioblastoma, renal cell carcinoma, phaeochromocytoma, or multiple pancreatic and renal cysts).

The central nervous system and ocular vascular tumours are similar in histological appearance and are best classified as haemangioblastomas.[5] They are composed of vascular endothelial lined channels separated by masses of vacuolated foam cells. Three main cell types are recognised in the tumour: endothelial cells, pericytes, and lipid laden interstitial stromal ('foam') cells.[5–11] In contrast to normal retinal capillaries the tumour endothelial cells are fenestrated,[8,11] which is in keeping with the clinical findings of retinal vascular exudation. Despite the many histological and electron microscopic studies the cellular origin of the retinal tumours and, in particular, the interstitial 'foam' cells remains controversial.[5–11] It has been suggested that these may derive from astrocytes,[5,7] neuroendocrine cells,[10] or primitive vascular stem cells.[11] Immunohistochemical studies of retinal tumours are also inconclusive.[5,10,11]

The retinal and optic nerve haemangiomas seen in VHL disease are of two clinical types. Endophytic tumours arise from the superficial retina or anterior surface of the optic disc and grow inwards towards the vitreous where they are seen as elevated red vascular tumours. There is great variation in size and larger peripheral retinal tumours usually have a dilated feeding arteriole and draining vein. Early tumours, seen as tiny capillary dilatations, may be easily missed on ophthalmoscopy but are usually readily apparent on fluorescein angioscopy or angiography.[4,12,13] Visual loss may occur secondary to exudative or tractional retinal detachment, vitreous haemorrhage, macular oedema, or epiretinal membrane formation causing macular distortion. Less commonly, exophytic tumours may arise from the outer retinal layers; they tend to occur in the peripapillary retina and often lead to difficulties in diagnosis.[14,15] The usual presentation is with central visual loss and fundus examination usually reveals retinal oedema and exudates but without any visible angioma. They may be mistakenly diagnosed as papilloedema, peripapillary disciform, or juxtapapillary choroiditis.[14] The diagnosis is usually made on stereo fluorescein angiography which demonstrates a deep retinal angioma which fills early in the arterial phase. The angioma often shows a dual circulation from both the ciliary and superficial retinal vessels.[14,15]

The lack of reliable information about the natural history of untreated retinal angiomas makes it difficult to recommend a rational treatment protocol. Furthermore with large angiomas the complications of treatment may be similar to those of the tumour itself and it may be difficult to assess the efficacy of the treatment. Although some tumours may show spontaneous regression[16] most do not. Management depends mainly on the size and site of the tumour. Peripheral angiomas respond well to treatment especially if they are small but the results of treatment of optic disc and peripapillary exophytic tumours are still disappointing.[14,15] Many different treatment modalities including cryotherapy,[4,12,17] diathermy,[17] xenon arc photocoagulation,[12,17] laser photocoagulation,[14,15,18–20] radiotherapy,[21,22] and local resection[23] have been used. Small peripheral angiomas (<3 mm) are best treated with argon laser photocoagulation[18–20] which may be combined with intravenous fluorescein to increase laser uptake.[20] More than one treatment session may be necessary. Cryotherapy is used for larger peripheral tumours, those with extensive subretinal fluid, or those arising close to the ora serrata. In tumours not responding to cryotherapy, irradiation[22] or local excision[23] may be used. Experience with these latter modalities is limited however. Large tumours, or their response to treatment, may cause vitreous haemorrhage, exudative retinal detachment (which may take months to resolve after treatment), and epiretinal fibrosis. These complications may require vitreoretinal surgery once the tumours have regressed. Treatment of optic disc and peripapillary exophytic lesions is not indicated unless there is already visual loss. Results of laser photocoagulation are disappointing[14,15,24] and radiotherapy, using newer lens sparing techniques,[21] may offer an alternative approach. However, some patients will show relentless progression of their tumour and visual loss despite treatment. Prognosis is best for small peripheral tumours and visual screening programmes should identify retinal angiomas at an early stage when treatment is effective.[13]

All affected patients require lifelong ophthalmic follow up and annual investigation for extraocular complications. The cumulative risk of a VHL disease patient developing a retinal angioma, cerebellar haemangioblastoma, and renal cell carcinoma at age 30 years are 44%, 38%, and 5% respectively, rising to 84%, 70%, and 69% respectively at age 60 years.[1] It follows that the majority of patients with VHL disease will develop a renal cell carcinoma if they live long enough, and renal cell carcinoma is now the most common cause of death

Table 1 Cambridge screening protocol for VHL disease in affected patients and at risk relatives. These guidelines are for asymptomatic individuals; symptomatic patients should be investigated urgently. The frequency of screening may be reduced in relatives in whom DNA linkage studies reduce their risk

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Affected patient
(1) Annual physical examination and urine testing.
(2) Annual direct and indirect ophthalmoscopy with fluorescein angioscopy or angiography.
(3) Magnetic resonance imaging (MRI) (or computed tomography (CT)) brain scan every 3 years to age 50 and every 5 years thereafter.
(4) Annual renal ultrasound scan, with CT scan every 3 years (more frequently if multiple renal cysts present).
(5) Annual 24 hour urine collection for VMAs (vanillyl mandelic acids).

At risk relative
(1) Annual physical examination and urine testing.
(2) Annual direct and indirect ophthalmoscopy from age 5. Annual fluorescein angioscopy or angiography from age 10 until age 60.
(3) MRI (or CT) brain scan every 3 years to from age 15 to 40 years and then every 5 years until age 60 years.
(4) Annual renal ultrasound scan, with abdominal CT scan every 3 years from age 20 to 65 years.
(5) Annual 24 hour urine collection for VMAs.

For full details see Maher *et al.*[1]

in VHL disease.[1] Patients with VHL disease are not only at greatly increased risk of tumour development, but, as with other inherited cancers such as retinoblastoma, are predisposed to develop multiple tumours and at a younger age than sporadic cases.[25] The majority of patients with central nervous system haemangioblastoma have, or will develop, multiple tumours and, similarly, 50% or more of patients with renal cell carcinoma have bilateral or multicentric cancers. Presymptomatic diagnosis of retinal angiomas and extraocular complications of VHL disease significantly reduces morbidity and mortality. The Cambridge screening protocol is shown in Table 1. Systematic ophthalmic and systemic screening of asymptomatic patients and relatives is important and worthwhile. We detected asymptomatic retinal angiomatosis in 60% of affected patients with no previous ophthalmic investigation and 30% of asymptomatic at risk relatives had subclinical evidence of VHL disease.[13] While screening of relatives at risk of developing VHL disease is productive and cost effective, the efficiency of screening would be enhanced by the presymptomatic diagnosis of gene carriers. This would allow low risk individuals to be reassured and screened less frequently.

The mapping of the gene for VHL disease to the short arm of chromosome 3 opened the way for the development of presymptomatic diagnosis using linked DNA markers.[26] The VHL disease gene has now been mapped to a small region at the tip of the short arm of chromosome 3 and close flanking markers (that is, either side of the gene) identified.[27-29] An important finding has been that although there are clear interfamilial differences in the clinical manifestations of VHL disease (for example, risk of phaeochromocytoma) all available evidence points to there being only a single gene for VHL disease.[27-29] This has enabled two groups to demonstrate that presymptomatic diagnosis of VHL disease using linked DNA markers is possible in the majority of families with suitable structure.[30,31] However this form of analysis is not possible for relatives of isolated cases. The isolation and characterisation of the gene for VHL disease would be a major breakthrough in understanding the pathogenesis of this disorder and increasing the availability of presymptomatic diagnosis. There is statistical, cytogenetic, and molecular genetic evidence that the VHL disease gene functions as a tumour suppressor gene of the retinoblastoma type.[25,32] Chromosome 3p allele loss is a frequent finding in many non-inherited human cancers including renal cell carcinoma. If the VHL disease gene does prove to be similar to the retinoblastoma gene then it is likely that it will be implicated in the pathogenesis of sporadic tumours in addition to VHL disease neoplasms.

Almost 100 years ago Treacher Collins[33] described familial retinal angioma. Since then more than 700 patients with what subsequently became known as VHL disease have been reported. In recent years, improved knowledge about the natural history has led to the recognition of the importance of ascertaining and screening patients and at risk relatives. In addition, advances in molecular genetics are now facilitating the management of families with VHL disease by enabling presymptomatic diagnosis in many cases. Research groups in the United Kingdom and United States are closing in towards isolating the gene and it is hoped that the VHL disease gene will have been analysed by the anniversary of Treacher Collins' description.

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Details of a national register for VHL disease families and of molecular genetic investigations are available from Dr E R Maher, Department of Clinical Genetics, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK.

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CASE REPORTS

Horner's syndrome: an electron microscopic study of a human iris

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Abstract

Electron microscopy was performed on the irides of a man with a history of a long standing Horner's syndrome which resulted in iris heterochromia. Comparison of his normal brown iris with the depigmented blue iris showed depletion of anterior border cells and absence of sympathetic nerve fibres. Stromal melanocyte numbers were also diminished but melanosome numbers within the residual cells were not significantly different. Postnatal maintenance of stromal and anterior border zone pigmentation, derived from the neural crest, would appear to be dependent on an intact sympathetic nerve supply in contrast to the iris pigment epithelium which remains normally unaffected in Horner's syndrome.
(*Br J Ophthalmol* 1992; 76: 746–749)

The association of paresis of the cervical sympathetic nerve supply with heterochromia of the iris in Horner's syndrome was described by Calhoun in 1919, who reported his series of experiments on rabbits and other rodents, and showed that depletion of iris pigmentation was related to length of survival after sympathectomy.[1] He compared his results in animals with data from humans, noting especially the effects of forceps delivery in the induction of Horner's syndrome which had been described in 1875, as consisting of ptosis, miosis, anhidrosis, and facial hemiatrophy. At the time of his paper there had been no histopathological examination of a human decolorised iris and such specimens remain rare. This paper describes the ultrastructural changes in one such case.

Case history

In November 1988 a 65-year-old man was admitted for repair of a thoracic aortic aneurysm. He was noted to have a left Horner's syndrome with iris hypochromia thought to have been present since birth. His obstetric and neonatal history were not available. There were no associated relevant neurological findings.

Postoperatively the patient failed to recover consciousness. Computed tomographic scanning revealed multiple infarcts throughout the cerebral hemispheres, the cerebellum, and brainstem. Repeated neurological examination failed to show any improvement and, at the request of the family, the patient was extubated during the fourth postoperative week. He died shortly thereafter.

Formal pharmacological testing was carried out during the postoperative period. Testing with 4% cocaine confirmed the left sided Horner's syndrome, with failure to dilate to hydroxyamphetamine suggesting a postganglionic lesion. Supersensitivity to phenylephrine and facial anhidrosis were not investigated.

Histopathology

After removal of the corneas for donor material, the eyes were fixed in glutaraldehyde and sections were taken. The normal right eye was a light brown colour with several freckles of a deeper brown hue. The left affected eye had a pale blue grey iris, with a focal area of browner colour around the pupil and three prominent iris naevi (Fig 1A and B). Sections were taken from the normal brown eye, the blue areas of the affected eye, the slightly more normochromic area of the affected eye and the iris naevi. Light and transmission electron microscopy (TEM) were carried out.

Iris pigmentation is conferred by the cells of the anterior border and stroma. Heterochromia may arise either as a result of reduction in the number or volume of melanocytes, or the number or volume of the specific organelles (the melanosomes) within those cells.[2] Quantitation of the number of pigmented melanocytes in the anterior border and stroma was performed by computerised image analysis and comparisons were made between the normal contralateral brown iris and the blue and brown areas in the affected iris. The number of clump cells was also measured. Using electron microscopy at a magnification of 1200, the number and size of the melanosomes per unit volume of melanocyte cytoplasm were measured. TEM was also used to search for the presence of axons within the iris, especially in the anterior border in juxtaposition to melanocytes.

The iris pigment epithelium was also examined in each eye.

Results

Melanocytes in the anterior border and stroma were greatly diminished in the affected left eye compared with the normal right brown eye. This can be seen in the photomicrographs of the

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Figure 1 (A) Affected 'blue' eye: note miotic pupil, with focal peripupillary retention of original colour and three iris naevi. (B) Unaffected 'control' brown eye with unconstricted pupil and well defined iris collarette.

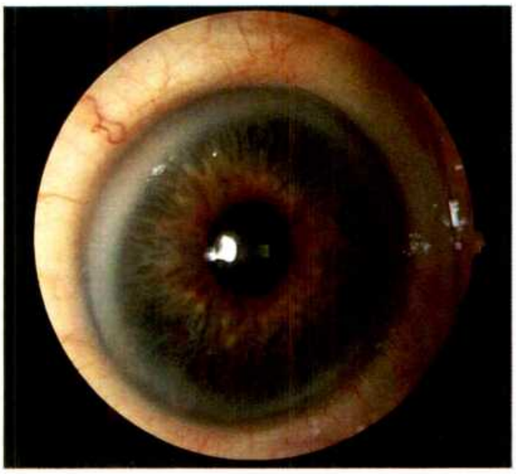


Fig 1A

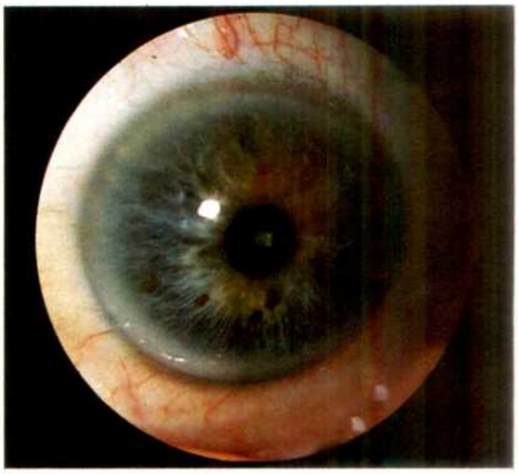


Fig 1B

toludine blue stained semi-thin sections taken at the same magnification (Fig 2A and B).

Quantitative image analysis shows that the number of cells in the anterior border per mm in the 'blue' anterior border of the affected eye is equivalent to 3204/mm^2 and in the unaffected eye 8005/mm^2. There was also a decrease in the number of stromal melanocytes. The number of cells in the stroma was 1380/mm^2 in the normal eye which is within the range of values which gave a mean of 1031/mm^2 in a previous set of irises used as controls.[2] The number of stromal cells in the affected iris of this patient was 349/mm^2.

Both the anterior border and the stroma therefore showed a fall in the number of pigmented cells.

The apparent volume of cytoplasm of these cells did not appear to alter, the cells were of the same shape although fewer in number (Fig 3A and B). (The rounding up of processes was not as marked as in Fuchs' heterochromia.) The mean number of melanosomes was 44·6 (SD 2·1) per cell in the affected eye compared with 50·1 (SD 2·3) in the control eye.

There were three naevi in the affected iris. These appeared to contain more cells per mm^2 and the number of melanosomes per cell was slightly increased at 55 per cell. They also contained fewer type III (slightly immature) melanosomes than the brown eye melanocytes. Both normal and affected eyes contained clump cells (macrophages that engulf liberated melanin); these contained both small melanosomes derived from cells of neural crest origin (anterior border and stromal cells) and also large melanosomes from iris pigment epithelial cells, as well as lipid laden phagosomes (Fig 4). The iris pigment epithelial cells did not differ in the two eyes.

Axons were demonstrably entwined amongst the processes of the anterior border cells in the unaffected eye but not in the affected eye. They could be recognised by granulated vesicles similar to those illustrated by Mukano,[3] and conformed to his description of adrenergic nerves though there was some loss of cellular architecture owing to slightly delayed fixation (Fig 5). Myelinated nerve fibres were present in both eyes (Fig 6).

There was therefore a decrease in the number of melanocytes present in the anterior border and stroma of the affected eye and a slight reduction in the number of organelles. There was also an apparent lack of sympathetic axons.

Discussion

This patient had a Horner's syndrome with depigmentation of the affected iris. We do not know that it was of congenital origin but it had been present for at least 40 years. The diagnosis was confirmed pharmacologically and testing with hydroxyamphetamine showed no reaction, suggesting a postganglionic localisation of the lesion. The interpretation of pharmacological tests in congenital Horner's syndrome is complicated by trans-synaptic degeneration and must

Figure 2 Semi-thin sections of affected (A) and control (B) iris showing reduction in numbers of anterior border cells and stromal melanocytes in affected eye. Toludine blue ×75.

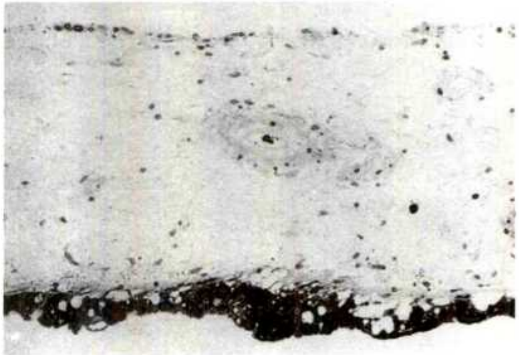


Fig 2A

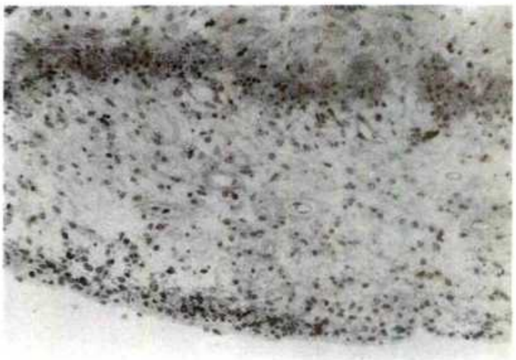


Fig 2B

Figure 3 Electron micrographs of anterior border of affected (A) and control (B) iris showing atrophic anterior border with fewer cells and no evidence of complex interdigitations in (A) when compared with (B). Cells and nuclei are of similar size but a clump cell is present in the lower right hand corner of (A) the affected iris.

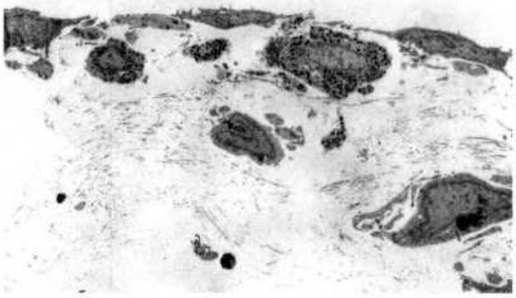


Fig 3A

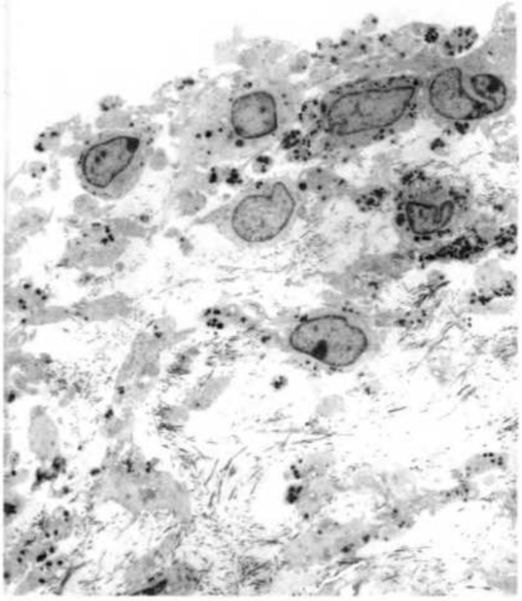


Fig 3B

be interpreted in the light of the clinical history and distribution of anhidrosis.[4] These authors suggest that heterochromia in congenital Horner's syndrome is a feature of a postganglionic lesion or a preganglionic lesion with trans-synaptic degeneration.

Pigmentation of the iris depends predominantly on the distribution of pigment within melanocytic cells on the anterior border and within the stroma. These cells are derived from the neural crest and migrate into the human iris late in gestation, and postnatally so that full pigmentation is not normally present until 9 months after birth. The iris pigment epithelium is derived from the primary optic vesicle and these cells and their much larger melanosome organelles are not dependent on the sympathetic nervous system and are present 6 weeks after conception. The migration of all neural crest cells is presumed to be preprogrammed but the end stage distribution and changes in cell shape from the spindled migrating cells to the sessile dendritic cells may be influenced by local trophic factors. Sympathetic control of migration and distribution of the cells responsible for skin pigmentation are not present in higher mammals, in contrast to amphibians and reptiles which can respond rapidly to threat, by camouflage. Strangely the trophic mechanism modulated by the sympathetic nervous system is retained within the eye, though swift changes of colour are not, of course, seen. Melanocytes of the eye are regarded as being continent in contrast to those of the skin as they do not donate melanin to other cells or shed it in cycles in response to actinic stimulation. Their tyrosine dependent metabolism is therefore reduced compared with skin melanocytes. Fading of iris colour occurs with age and heterochromia can arise as a result of inflammation.[2] Both migration and maintenance of neural crest derived iris pigment containing cells appear to be under sympathetic control since both congenital and acquired Horner's syndromes lead to lack or loss of colour within the affected iris, though this may take many years to develop with acquired lesions. Anomalous or neoplastic groups of anterior border cells forming naevi may be autoregulatory since persistent pigmentation has been described in the iris naevi of a patient with Horner's syndrome[5] as in our case. Sympathetic nerves were not seen in association with the naevi in our case.

Though there are numerous clinical descrip-

Figure 4 Another pair of clump cells, close to the anterior border in the brown control eye, containing lipid filled phagosomes and melanosomes within vacuoles. The melanosomes are of both anterior border or stromal melanocytic origin and a large pigment epithelial melanosome is also present. The complex interdigitations of the anterior border cells, within which unmyelinated nerves lie are also seen. TEM ×3255.

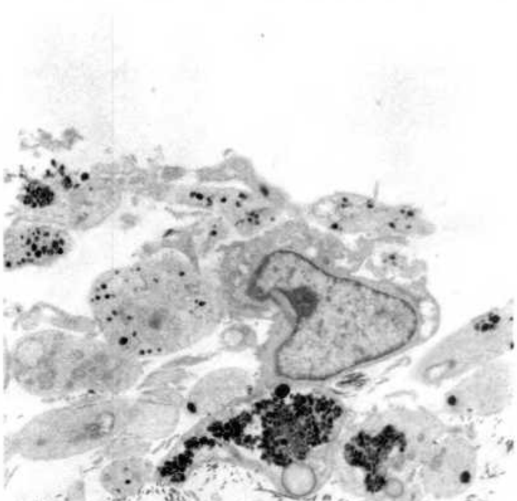
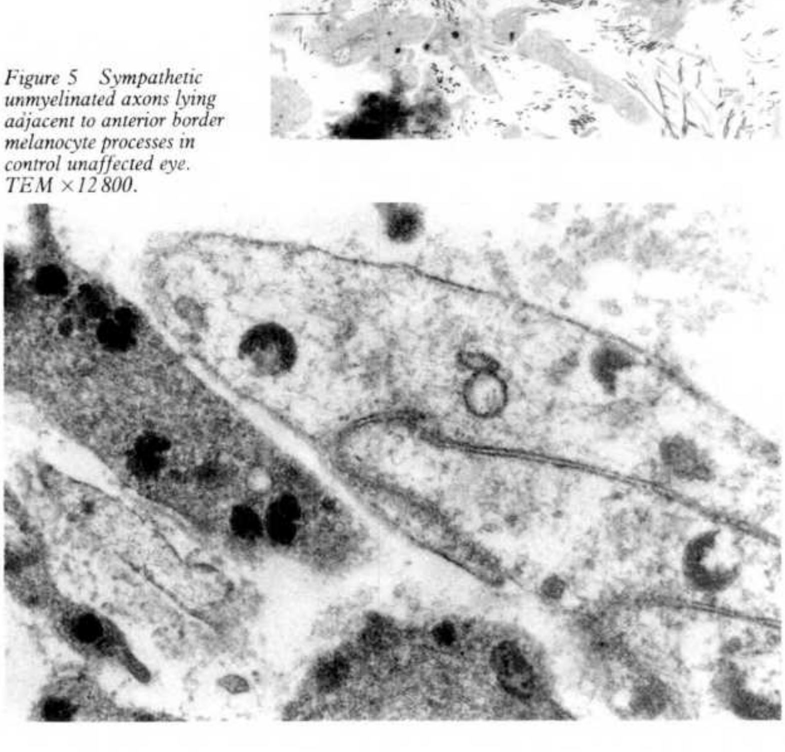


Figure 5 Sympathetic unmyelinated axons lying adjacent to anterior border melanocyte processes in control unaffected eye. TEM ×12 800.



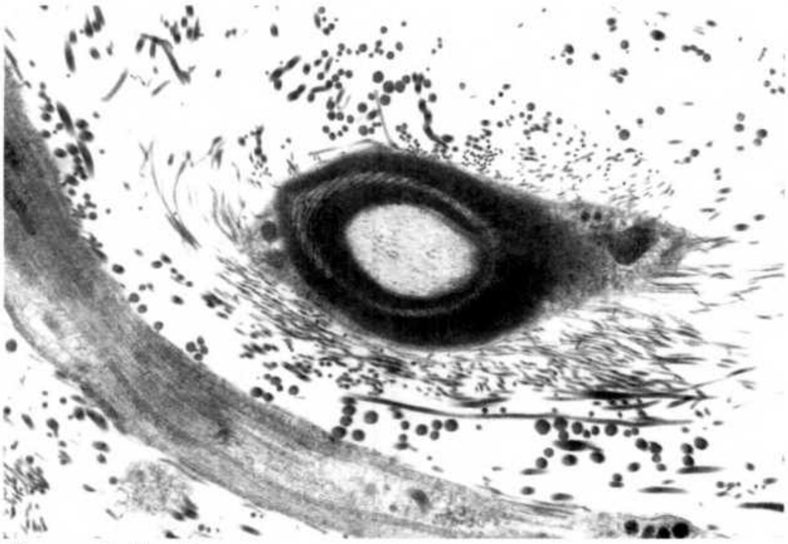


Figure 6 Myelinated nerve in stroma of control eye. Similar fibres were present in the affected eye. TEM ×5300.

tions of the effects of sympathetic denervation of the iris, histopathologic descriptions are rare on human material and most observations have been on animal models.[6] Calhoun quotes the work of Bistis who examined four rabbit eyes[7] and showed that there was reduction of stromal pigmentation with rounded or oval nuclei after sympathectomy. Both Laties[8,9] and Ringvold[10] show that in animals there is an intimate spatial relationship between the adrenergic neurons and iris melanocytes, especially those on the anterior border of the iris. Mukano[3] has shown in an electron microscopic study of the nerve terminals to normal melanocytes in the stroma of the normal iris, that there are four different types of terminal present. Those associated with the sympathetic nervous system consist of granulated or empty vesicles 60–110 nm in diameter separated by a basement membrane lying about 75 nm from the melanocytes and others more intimately associated with melanocytes only separated by a 25 nm gap. Two further types of terminal, thought to be parasympathetic, were also observed. Vasoactive intestinal peptide nerve fibres are also present,[11] probably running co-axially. Pharmacologically the action of the α adrenergic receptors appears to be more important than the β.[12]

Our results show that there is an apparent absence of sympathetic neurons in the affected eye as would be expected, and that there is a decrease in the number of cells derived from the neural crest but not of intracellular organelles. This may be due to a failure of cellular migration if the denervation occurred at or about the time of birth as seems possible, but there must have been some migration otherwise no pigmented cells would have been present. Another explanation would be that failure of sympathetic innervation leads to attrition of the normal cell population, but this is unlikely as hypochromia only occurs mildly and after many years with acquired Horner's syndrome whereas it is seen in infants with congenital Horner's syndrome. Active cellular loss, however, may be occurring since clump cells were normal or possibly slightly increased in number suggesting increased turnover, or greater cell loss on the affected side.

There were three naevi present and these were heavily pigmented. These may represent clumping of cells that were in the process of migrating but came to rest prematurely or they may represent an autonomous group of neoplastic cells which do not require the actions of the sympathetic nervous system to maintain their degree of pigmentation.

It is likely that this patient had a congenital partial post-ganglionic lesion followed by loss of normal postnatal migration. This would account for the widespread heterochromia as well as explaining the focal retention of pigmentation around the circumference of the pupillary margin. This latter area would contain the cells most likely to have migrated and subsequently become able to form pigment before denervation occurred leading to failure of pigmentation in the rest of the iris.

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Neurilemmoma of the anterior ethmoidal nerve encroaching upon the nasolacrimal duct

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Abstract

The clinical, light microscopic, ultrastructural, and immunohistologic findings of a neurilemmoma encroaching upon the nasolacrimal duct are presented. This is the first reported case of this rare tumour of the nasolacrimal duct where the diagnosis has been confirmed by electron microscopy and immunohistochemical techniques.

(*Br J Ophthalmol* 1992; **76**: 750–752)

Clinical history

A 72-year-old white diabetic female complained of chronic epiphora of the left eye of 1 year's duration and a growing mass nasal to the medial canthus of the left anterior orbit of 8 years' duration (Fig 1). The patient denied any history of diplopia proptosis, orbital pain, trauma, sinusitis, or inflammation. Personal and family history were negative for *café au lait* spots and neurofibromas. Past medical history was notable for insulin-dependent diabetes mellitus of 30 years' duration, for which the patient was on a regimen of insulin and isophane insulin injections. Surgical history was notable for cataract extraction and intraocular lens implantation in the right eye 2 years previously and laser photocoagulation for diabetic retinopathy in the right eye.

On examination the best corrected visual acuity was 20/80 OD, 20/60 OS. On palpation a large, firm, movable, ovoid mass was felt, with no expression of fluid on compression of the nasolacrimal duct. Irrigation revealed a partial obstruction to flow beyond the common canaliculus. Dacryocystography revealed the nasolacrimal duct to be displaced anteriorly and flattened by a round, well-circumscribed mass located directly behind the sac (Fig 2). The mass partially obstructed the nasolacrimal duct as evidenced by a limited amount of contrast medium entering the nose and pharynx, with splaying of contrast medium over the nasolacrimal mass on the 25 minute film.

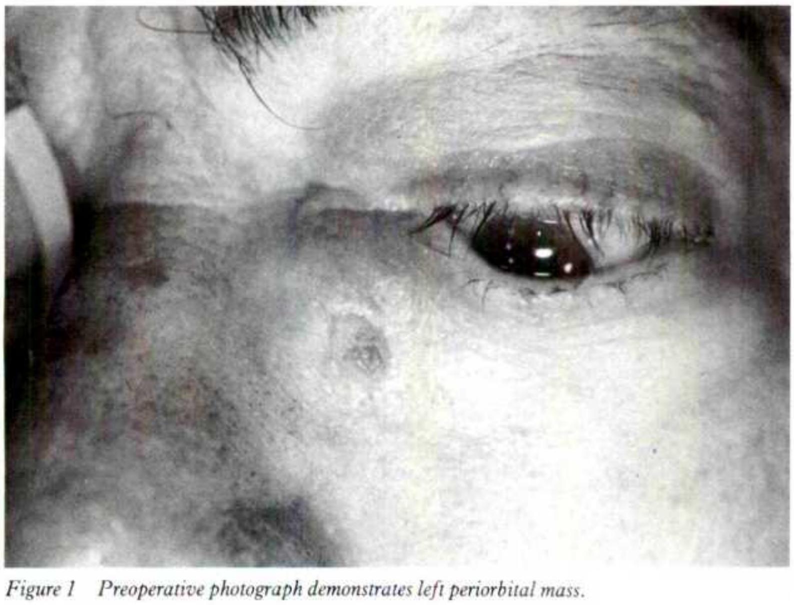

Figure 1 Preoperative photograph demonstrates left periorbital mass.

Surgical exploration under general anaesthesia via an incision over the anterior lacrimal crest revealed a solid, well-circumscribed, encapsulated lesion completely filling the nasolacrimal duct (Fig 3).

Intraoperative frozen section showed a spindle cell tumour. The lesion appeared to arise from a nasal branch of the anterior ethmoidal or infraorbital nerve supplying the nasolacrimal duct. The tumour was removed in its entirety; it measured approximately 1·5×2·5 cm. Probing demonstrated a stenotic upper and a partially obstructed lower lacrimal system. Silastic intubation was performed and the residual dome of the sac was used to complete a modified Illif dacryocystorhinostomy. The patient tolerated the procedure well and had an uneventful recovery, with complete resolution of epiphora.

Pathology

Histological examination revealed a spindle cell neoplasm, arranged in bundles and fascicles with foci of increased cellularity, suggestive of palisading (Fig 4). Mucoid degeneration, microcyst formation, and calcification were absent. Tumour cell nuclei were 'wavy' and in some areas 'tear drop' shaped with rare mitoses. Blood vessel walls appeared thickened due to hyalinisation. The histopathological differential diagnosis included neurilemmoma, leiomyoma, and neurofibroma.

Electron microscopy (EM) demonstrated spindle cells with intracellular granules, possible basement membrane formation, and minimal rough endoplasmic reticulum (Fig 5). Immunoperoxidase staining showed tumour cell expression of S-100 protein and vimentin (Fig 6). Staining for desmin, muscle actin, smooth muscle actin, and neuron-specific enolase were negative. Given the histology, EM features, and characteristic immunohistochemical staining, the diagnosis of neurilemmoma was made.

Discussion

Neurilemmoma is a benign nerve sheath tumour of Schwann cell origin which is rare in the orbit. In a review of the literature between 1935 and 1963 by Schatz,[1] only 25 benign neurilemmomas and 14 malignant neurilemmomas were reported out of 2196 case of unilateral exophthalmos or

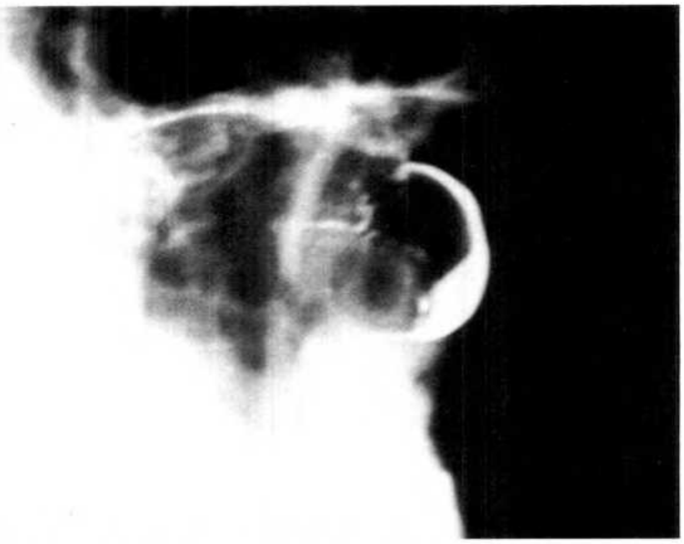

Figure 2 Dacryocystogram reveals anterior displacement, flattening, and partial obstruction of nasolacrimal duct by rounded posterior mass.

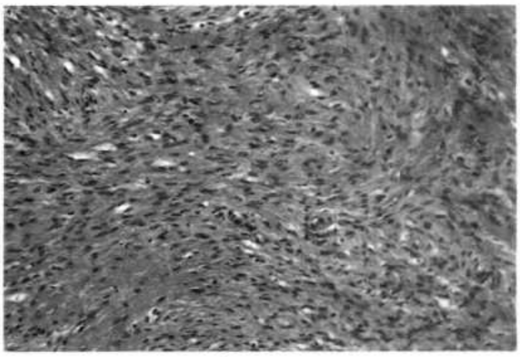

Figure 4 Characteristic palisading (Antoni A) pattern of spindle cell neoplasm, with cells arranged in bundles and fascicles with foci of increased cellularity (haematoxylin and eosin, ×55).

orbital tumours. Neurilemmoma accounts for approximately 1% of orbital neoplasias.[1-4] It is known to be a tumour of adulthood, though the age of onset may range from 20 to 70 years. No sex predilection has been shown.

Neurilemmoma usually arises from branches of the supraorbital or supratrochlear nerves, less commonly it may arise from the infraorbital, ciliary, oculomotor, trochlear, or abducens nerves.[5] Non-orbital cases have been reported rarely arising from the lid, conjunctiva, limbus, sclera,[6,7] ciliary body,[8] and choroid.[9]

Only one other case of neurilemmoma arising from the area of the nasolacrimal duct has been reported.[10] In that case, however, the diagnosis was based solely on light microscopy without immunohistochemical staining or EM confirmation and no reference was made as to the probable nerve of origin. In our case, diagnosis was based on the characteristic gross, light microscopic, EM, and immunohistochemical appearance of the tumour, which intraoperative dissection showed as arising from a nasal branch of the anterior ethmoidal or infraorbital nerves supplying the nasolacrimal duct. In 17 cases of neurilemmoma, reviewed by Dervin *et al*, none presented with epiphora though 41% were located in the lower nasal quadrant.[11]

As in our case, neurilemmomas are usually solitary, well-encapsulated tumours of round, ovoid, or fusiform shape.[1,3,5,10] Histologically, neurilemmomas are composed of spindle shaped cells which may be arranged in either an Antoni A (palisading) or Antoni B (mucoid degeneration) pattern, the former being the more common. The Antoni B pattern may be associated with central areas of central haemorrhage or calcification within the myxoid stroma.

The EM appearance of neurilemmoma is thought to be characteristic. Spindle cells with intracellular granules, basement membrane formation, and minimal rough endoplasmic reticulum are the rule. Extracellular collagen with foci of long-spacing collagen ('Luse bodies') may also be present.[8,12,13]

Immunohistochemical stains are useful to differentiate neurilemmomas from tumours of similar light microscopic appearance. Neurilemmomas characteristically express S-100 protein and vimentin.[14] In contrast to leiomyomas, neurilemmomas stain negative for desmin, muscle actin, and smooth muscle actin.

The differential diagnosis between neurilemmoma and neurofibroma is more difficult to make using histochemical techniques. While neurofibromas stain positive with Alcian blue, neurilemmomas may stain either Alcian blue positive or negative, depending on whether they are of the Antoni A or B types, respectively. More useful in the case of Antoni A neurilemmomas is their gross and light microscopic appearance, which is typically well-encapsulated and arranged in an orderly palisading fashion, unlike neurofibromas.

In our case, the diagnosis of leiomyoma was

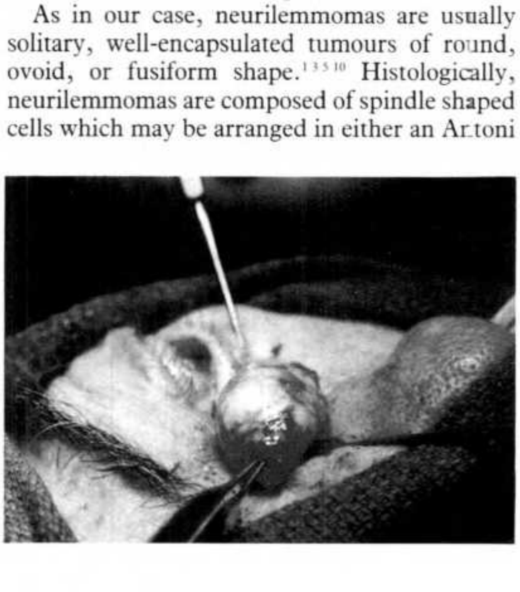

Figure 3 Intraoperative photograph of solid, well-circumscribed, encapsulated lesion completely filling nasolacrimal duct.

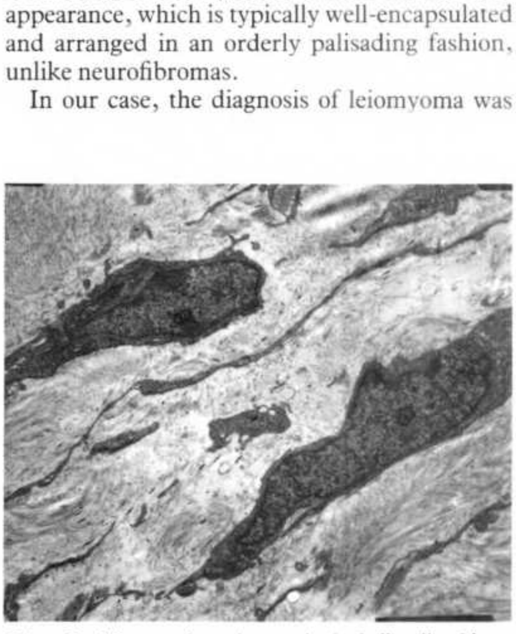

Figure 5 Electron photomicrograph of spindle cells with intracellular granules, possible basement membrane formation, and minimal rough endoplasmic reticulum.

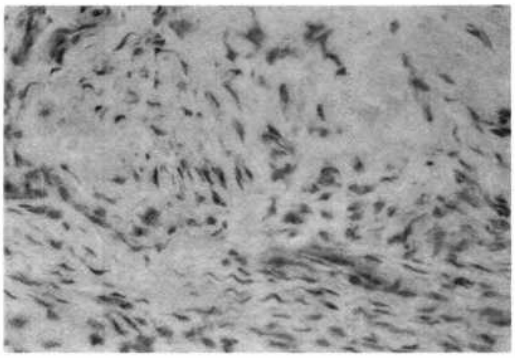

Figure 6
Immunoperoxidase staining reveals tumour expression of S-100 protein and vimentin.

unlikely given the negative staining for muscle actin and smooth muscle actin, as well as the 'wavy' and 'tear drop' shaped nuclei with rare mitoses. Though the immunoperoxidase staining pattern was consistent with either neurofibroma or neurilemmoma, the well encapsulated nature of the lesion and palisading histology made for the diagnosis of neurilemmoma.

The clinical presentation and features of neurilemmoma are variable. Neurilemmomas are usually unilateral, slow-growing, and non-invasive.[1 5 10] Orbital neurilemmomas often present with exophthalmos, decreased visual acuity, pain, or diplopia. Findings may include ophthalmoplegia, pupillary involvement, and fundus changes, such as disc oedema or optic atrophy.[2] Extraorbital neurilemmoma may have similar signs and symptoms depending upon anatomical involvement. In both our case and the other reported case of neurilemmoma of the nasolacrimal duct, a presenting complaint was painless swelling nasal to the medial canthus of one eye. Our case differed, however, in that epiphora was also prominent.

Neurilemmomas are benign and do not metastasise, though malignant transformation has been known to occur very rarely. Lyons *et al* described three such cases.[15] Patients with highly cellular tumours or concurrent neurofibromatosis are at greater risk for malignant transformation, which may occur in up to 16% of these patients.[1]

The preferred treatment for neurilemmoma is surgical excision. Neurilemmomas are relatively radioresistant, so radiotherapy is reserved for refractory cases or palliation. Prognosis is good, especially in cases where early diagnosis allows for complete excision. Even when excision is incomplete recurrence is rare.[8] When recurrence does occur, it may be years after the original incision, and is usually local. The patient in our case remains asymptomatic 18 months following surgical excision with no signs of local recurrence.

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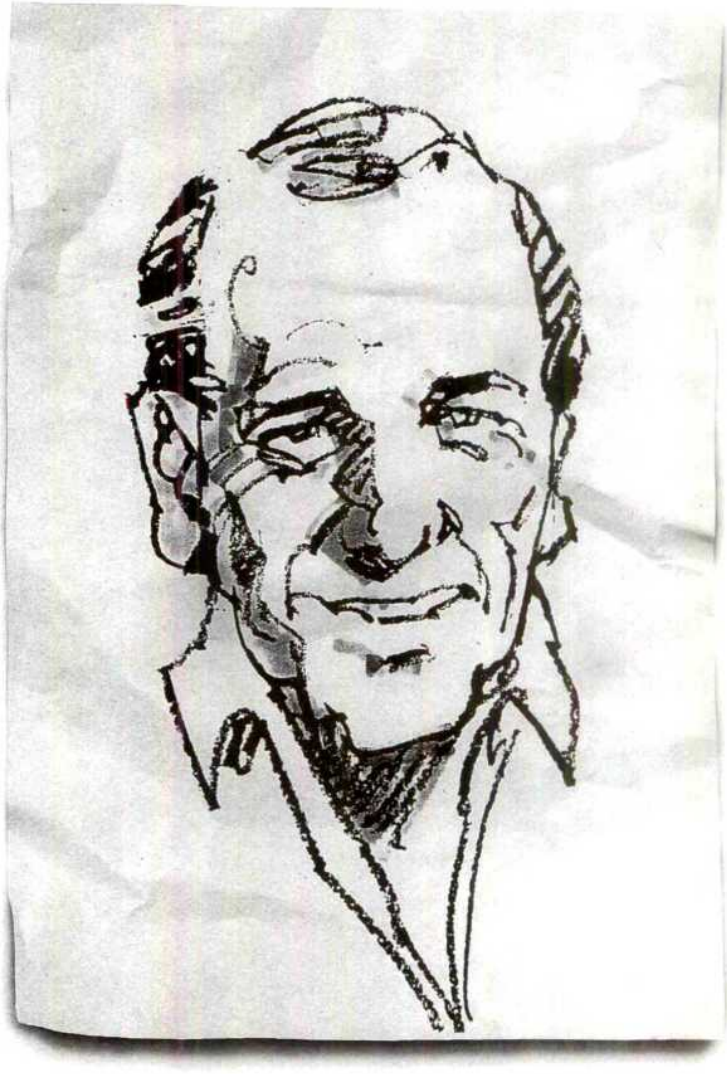

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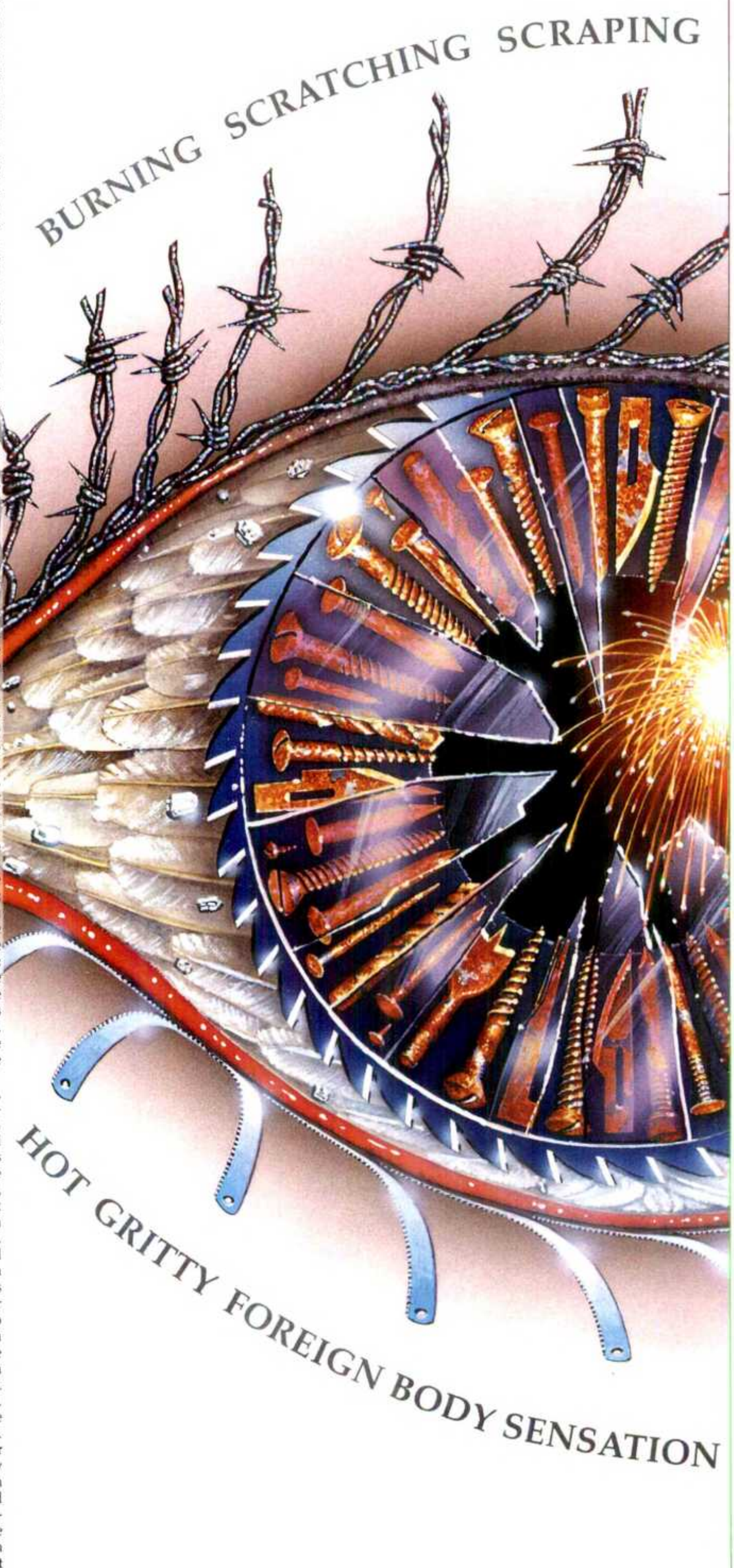
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British Journal of Ophthalmology 1992; **76**: 753–754

Anthrax of the eyelids

Abdelouahed Amraoui, Khalid F Tabbara, Khalid Zaghloul

Abstract

Anthrax is a disease caused by *Bacillus anthracis*. The disease affects primarily herbivores including sheep, cattle, horses, and other domestic animals. Humans may rarely be affected. We examined one male and two female patients with a localised itchy erythematous papule of the eyelid. A necrotising ulcer formed in each of the three cases resulting in a black lesion. Scraping in each case showed Gram positive rods and culture grew *Bacillus anthracis*. All three patients responded to the intravenous administration of penicillin G, and the lesion resolved leaving scars in two cases. Anthrax is a rare disease but should be considered in the differential diagnosis of ulcers or pustules of the eyelids.

(*Br J Ophthalmol* 1992; **76**: 753–754)

Anthrax is a disease of herbivores caused by *Bacillus anthracis*. Humans become infected as they come into contact with infected animals or animal products.[1] Cutaneous anthrax accounts for the majority of cases[2 3] but oropharyngeal anthrax may appear.[4] The clinical presentation is characteristic: infection begins as a small itchy papule that enlarges within 24–48 hours, developing into an ulcer surrounded by vesicles. A black, necrotic, central eschar then forms, which is characteristic of the disease. Oedema is often striking, especially if the lesion is situated on the face. Lymphangitis and regional lymphadenopathy may occur. The disease may be fatal in about 20% of the cases if untreated.

We report three cases of anthrax of the skin of the eyelids.

Case reports

CASE 1

A 32-year-old female farmer noted a small erythematous papule in her left lower eyelid. This was followed by a vesicular eruption and eschar formation 8 days prior to admission. On examination the patient was found to have diffuse oedema of the left upper and lower eyelids with inability to open the eye. The left lower eyelid showed a black eschar with a plaque and slight ectropion (Fig 1). Visual acuity and the remainder of the ocular examination were normal.

Scrapings of the lesion revealed Gram positive rods, and culture yielded *Bacillus anthracis*. The patient was started on systemic penicillin G, 10 million units intravenously per day for a period of 7 days. The lesion resolved, with persistent cicatricial ectropion of the left lower eyelid (Fig 2). A biopsy specimen of the cutaneous lesion was subjected to histopathological evaluation.

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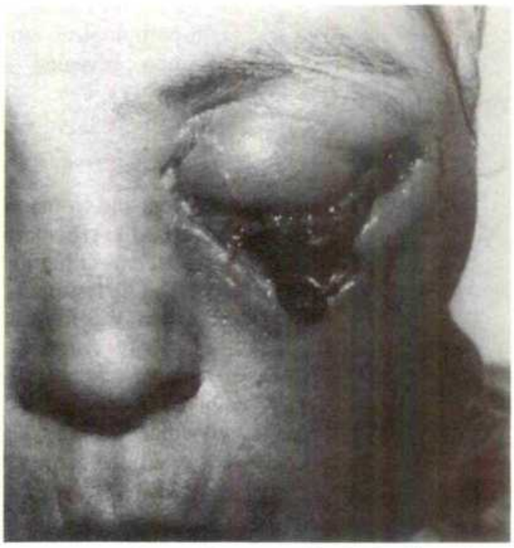

Figure 1 A 32-year-old woman with a dark eschar and ectropion of the left lower eyelid. Culture grew Bacillus anthracis.

This revealed a localised nodular granuloma and Gram positive rods.

CASE 2

A 43-year-old male presented with a history of a localised cutaneous lesion of the left eyelid of 15 days' duration. The patient gave a history of a small erythematous papule which became vesicular and painful, and has been associated with severe pruritis. On examination the patient was found to have a black eschar of the left lower eyelid, measuring 2 cm in diameter, which was surrounded by multiple vesicles. Other findings

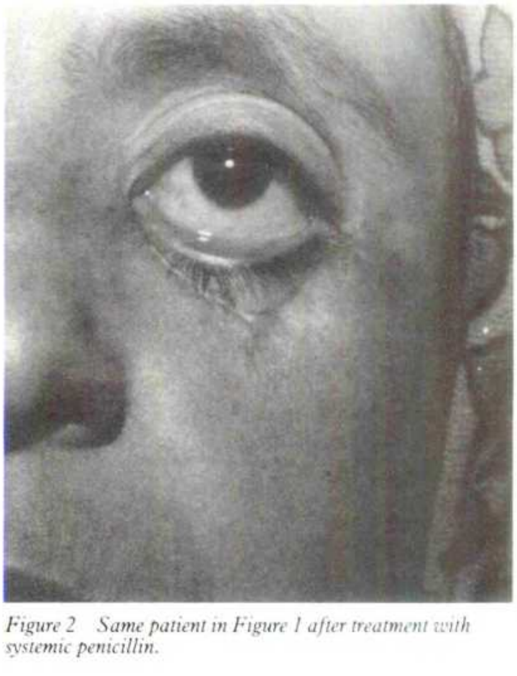

Figure 2 Same patient in Figure 1 after treatment with systemic penicillin.

in both eyes were normal. The patient had a temperature of 38°C. Scrapings of the eyelid revealed Gram positive rods, and culture revealed *Bacillus anthracis.*

The patient was admitted to hospital and was given 10 million units of penicillin G intravenously each day for a period of 7 days. The lesion healed completely within 10 days, leaving no clinical evidence of eyelid abnormalities. Histopathological studies of the lesion biopsy specimen revealed a chronic inflammatory reaction.

CASE 3

A 45-year-old woman presented with a history of a localised erythematous lesion of the left outer canthus, extending into the left upper and lower eyelids. The lesion was painful. On examination the patient was found to have a black eschar with necrosis of the upper and lower eyelids. The left cornea was normal but the anterior chamber showed flare and cells with evidence of posterior synechiae. Ophthalmoscopy of both eyes revealed normal optic nerve head, blood vessels, and retina. The right eyeball was normal.

Culture of the lesion grew *Bacillus anthracis.* The patient was treated with 10 million units of penicillin G given intravenously each day for a period of 7 days. She showed progressive improvement and complete healing of the skin lesion at the left outer canthus, associated with slight cicatrisation. The patient was seen again and had complete resolution of her uveitis in the left eye.

Discussion

Human infections are usually divided into two groups: agricultural and industrial. Our cases appeared to be agricultural infections as all persons involved were farmers who gave histories of contact with domestic animals. The ultimate reservoir of *Bacillus anthracis* is the soil. The organism has an ability to sporulate. Anthrax spores, however, do not give rise to cases of anthrax in animals, and a vegetative phase is required whereby the spores multiply and mature before animals can become infected. In countries where anthrax is enzootic, bones from animals may be contaminated with anthrax. This material is often used as fertiliser or as supplement to animal foods and has accounted for several human cases of cutaneous anthrax.

All three cases reported by us had localised itchy papules of the eyelid followed by a vesicular eruption and eschar formation. The treatment of anthrax with systemic penicillin is effective and was curative in all three patients. Anthrax is a rare disease but should be considered in the differential diagnosis of ulcers or papules of the eyelids. In case 3 there was, however, complete healing of the cutaneous anthrax of the patient's left outer canthus, and the uveitis in her left eye recovered completely following the systemic administration of intravenous penicillin G, and without use of topical steroids.

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British Journal of Ophthalmology 1992; **76**: 755–757

Bilateral Kimura's disease of the eyelids

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Abstract

A case of Kimura's disease affecting the eyelids bilaterally is reported in a 5-year-old boy of Afro-Caribbean extraction who has been followed for 12 years with repeat biopsies. He initially presented at 5 years of age with swelling of the left upper eyelid, left cervical lymphadenopathy, and eosinophilia. One year later he developed swelling of the right upper eyelid. There has been no change in the clinical appearance over the next 12 years. Repeated biopsies of the eyelids showed a diffuse inflammatory infiltrate with many eosinophils and lymphocytes. A lymph node biopsy showed reactive lymphoid hyperplasia. Immunohistochemistry using lymphoid markers showed a polyclonal pattern. Kimura's disease is a rare cause of eyelid swelling, particularly at such a young age and with bilateral involvement. This case demonstrates that bilateral orbital lymphoid lesions with cervical node involvement do not always imply lymphoma, but may have a benign pathogenesis. The unusually long follow up in this case confirms an excellent prognosis for Kimura's disease with conservative management. Accurate diagnosis in small orbital biopsies may spare the patient unnecessary radical surgery.

(*Br J Ophthalmol* 1992; **76**: 755–757)

Kimura's disease is a chronic inflammatory condition occurring predominantly in orientals, with occasional cases reported in Caucasians, and rarely in blacks.[1-5] To our knowledge it has not been reported previously in a person of Caribbean extraction. The first description appeared in the Chinese literature in 1937[1] as 'eosinophilic hyperplastic lymphadenopathy', but the disorder became popularly known as Kimura's disease following the report of Kimura *et al* in the Japanese literature.[2] Kimura's disease has a predilection for the head and neck region, but orbital involvement has been reported in only 14 cases.[5-11] Four of these patients had eyelid involvement.[5,6] In only one patient[5] was the disease bilateral. In the published literature on orbital disease there is little information on the long-term clinical behaviour or of the progressive histopathological changes which might occur. We had the opportunity to study repeat biopsies in the Afro-Caribbean boy over a period of 12 years and the findings are reported here.

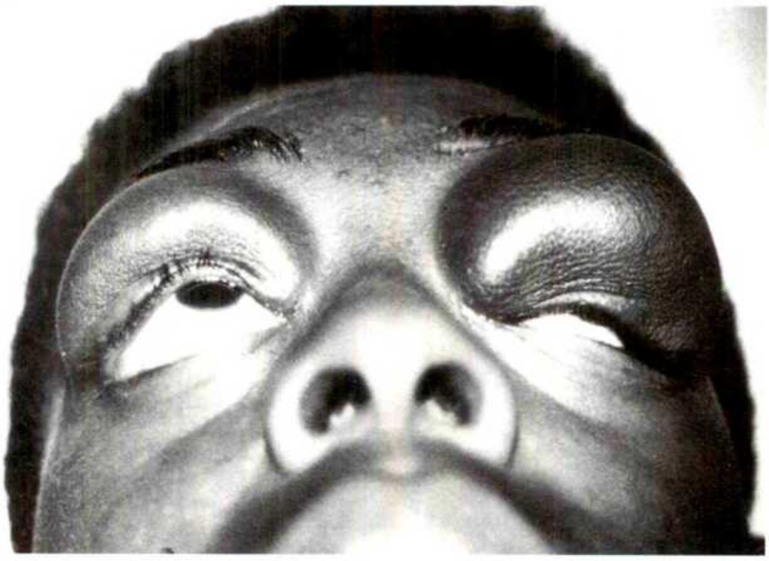

Figure 1 Clinical photograph of the patient showing bilateral swollen eyelids, more severe on the left.

Case report

A 5-year-old boy presented with swelling of the left upper lid and bilateral cervical lymphadenopathy. He was otherwise in good health and no other abnormalities were detected on ocular and general physical examination. Laboratory investigations included an ESR of 23 mm/hour, WBC of $10{\cdot}6\times10^9$/ml with a differential of neutrophils 42%, lymphocytes 41%, monocytes 3%, eosinophils 13%, and basophils 1%. The haemoglobin and platelet counts were normal. A biochemical profile, thyroid function tests, and serum calcium and albumin were normal. Serum electrophoresis showed a diffuse hypergammaglobulinaemia. HTLV 1 antibody titre was negative. An orbital computed tomographic (CT) scan showed diffuse swelling of the left lateral rectus muscle. A biopsy of the cervical lymph node showed a prominent eosinophilic infiltrate of follicles and interfollicular areas. This was interpreted as a benign inflammatory process. One year later swelling of the right eyelid became apparent. At that time both lids were almost symmetrically enlarged. The left eyelid was biopsied but there was no other surgical intervention. The child achieved normal growth and remained well despite the cosmetic handicap of grossly swollen eyelids. He noticed a variation in the size of his eyelids from day to day. At the age of 17, the patient was re-evaluated at his annual clinical examination. He was a healthy looking black male with massively swollen upper and lower eyelids (Fig 1). There was generalised swelling of the subcutaneous tissues of the eyelids, and firm discrete nodules were palpable, three on the right and two on the left (approximate maximal diameter 1 cm). All were freely mobile and non tender. One of the right upper lid nodules was biopsied. Physical examination revealed no lymphadenopathy or organomegaly.

Histopathologic findings

Biopsy of the left upper eyelid was performed at the age of 6 years. An inflammatory infiltrate composed of eosinophilic polymorphonuclear

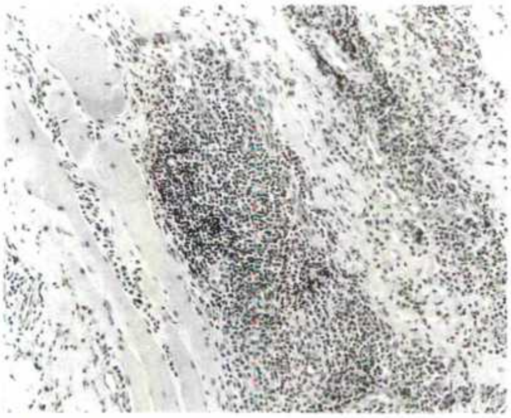

Figure 2 Extensive inflammatory infiltrate of striated muscle and fibroconnective tissue of the eyelid.

leucocytes, small lymphocytes, mast cells, and plasma cells was scattered throughout fibrous tissue and striated muscle (Fig 2). A few reactive lymphoid follicles were present. Degranulating eosinophils were particularly prominent around small blood vessels but there was no evidence of fibrinoid necrosis. The vessels had a slightly hyperplastic endothelial lining, but the epithelioid change and intracellular lumina which are typical of angioimmunoblastic lymphadenopathy were not seen (Fig 3). Clusters of eosinophils were present in the mantle zone of some follicles and occasional eosinophilic microabscesses were seen in the germinal centres (eosinophilic folliculolysis). The cervical lymph node showed follicular hyperplasia with multinuclear giant cells and eosinophils in germinal centres. Some eosinophils were degranulating. There was no evidence of atypia and Reed-Sternberg cells were not seen. Mitoses were confined to the germinal centres.

Biopsy of the right upper eyelid was performed 11 years later. It showed hyperplastic lymphoid follicles embedded in sclerotic fibroconnective tissue. The follicles were oval with a well defined eccentric mantle zone and prominent germinal centres. Polykaryocytes resembling Warthin-Finkeldy type giant cells were conspicuous (Fig 4) both in germinal centres and mantle zones. These giant cells contained up to 25 nuclei clustered together. Numerous eosinophils were present in the soft tissue and lymphoid follicles. Sheets of eosinophils, many degranulating, and small lymphocytes infiltrated striated muscle and fibrous tissues.

Immunohistochemical studies using monoclonal antibodies to B and T cell markers (L26 and UCHL1) and immunoglobulin (Ig) heavy and light chains (Dakopatts, Copenhagen, Denmark), the avidin-biotin-peroxidase complex (ABC) method of Hsu[12] and the Vector ABC kit (Vector Labs, Burlingame, CA, USA) revealed a polymorphic lymphoid infiltrate with the usual distribution of B and T cells. IgE staining was seen in lymphoid follicles and some plasma cells and mast cells. IgM and IgG positivity was also seen.

Discussion

Kimura's disease is an inflammatory process with a predilection for the head and neck region in young men histologically characterised by an angiolymphoid proliferation with eosinophilia and elevated serum immunoglobulin IgE.[1-6] The aetiology is unknown and controversy exists as to whether it represents a benign lymphoid neoplastic process or is an allergic reaction. Evidence concerning the long-term behaviour of the disease is scanty. Although some authors use the terms Kimura's disease and angiofollicular lymphoid hyperplasia interchangeably, recent studies suggest that they may be different entities.[12-15] Kimura's disease presents as a large solitary lump or multiple lumps, with an insidious onset, long duration, and a frequent occurrence of peripheral blood hypereosinophilia. Regional lymph node involvement occurs in up to 75% of cases. Systemic associations include asthma and the nephrotic syndrome.[6 14] Recurrence is common, estimated between 15% and 40% of cases,[15] but fatalities have not been reported. By contrast, angiolymphoid hyperplasia is said to present with small papules or nodules on the face and scalp. On histological examination prominent hypertrophic vessels with swollen endothelial cells proliferating around arterioles and venules are seen; lymphoid proliferation is less apparent. Systemic abnormalities are not frequent.

Although Kimura's disease is most often periauricular or submandibular, a small number of orbital lesions have been reported on the basis of an isolated biopsy and very few cases have

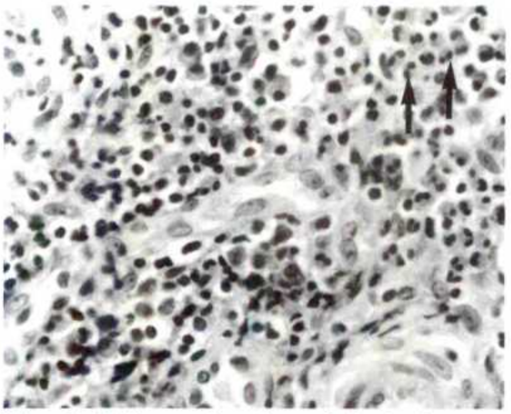

Figure 3 High power photomicrograph showing the predominance of the bilobed eosinophils (arrows) in the inflammatory infiltrate. A vessel with a hyperplastic endothelial lining is shown.

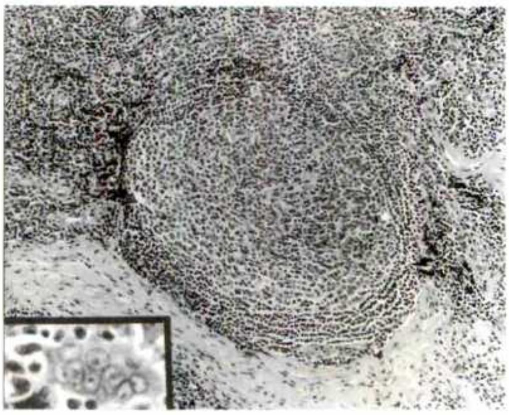

Figure 4 Haematoxylin and eosin stained section of the eyelid showing a hyperplastic lymphoid follicle, with a well delineated mantle zone. Warthin-Finkeldey type giant cells or polykaryocytes are shown in the inset.

been followed over prolonged time interval. The first orbital cases were recorded in 1976,[4] 1979,[5] and 1982[10]. In 1983, a series of five orbital and three adnexal cases was published,[6] including a previously reported case.[10] The mean age was 51 years (range 38–72), which is older than the mean age at other sites. Neither lid nor orbital disease have been reported in a child. The lesions were uniformly solitary and affected the eyebrow, superior orbital ridge, and roof of the orbit. The orbital nodules varied in size from 1·2 to 2·7 cm in maximal diameter. Those with an adnexal location comprised a solitary nodule at the inner canthus in one patient and the upper lid in two. These nodules were smaller (7–8 mm) than the orbital cases. Four orbital cases have been reported subsequently.[7–9 11] In one of these[8] the lesion arose in a patient who had undergone enucleation for malignant melanoma of the choroid, followed by an Iowa (polymethylmethacrylate) implant. The occurrence of Kimura's disease in this situation led the authors to suggest that the disease was a probable reaction to the implant. There have been no subsequent reports of Kimura's disease following orbital implants. The histopathological features described in the literature are similar to those seen in the present case – for example, eosinophilic infiltration of soft tissue, florid germinal centres, apparently increased postcapillary venules, and fibrous sclerosis. Giant cells of Warthin-Finkeldy type, which are more often associated with viral lymphadenopathies such as measles, were prominent in the germinal centres and the paracortex of our case. These cells have been noted by others in lymph nodes and salivary glands but not in the orbital cases affected by Kimura's disease.[15–18]

Ocular adnexal lymphoid proliferations can present clinical and histopathological problems and are well documented although there is much to learn. The finding of a mixed lesion composed of an eosinophilic and lymphocytic infiltrate, follicular hyperplasia, and fibrosis brings both orbital pseudotumour and Hodgkin's disease to mind. Inflammatory pseudotumours have a polymorphous inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes with a hyalinised or oedematous stroma. Endothelial cells are hypertrophied and prominent. Eosinophils may be present but are not usually such a conspicuous feature as in this case. Although lymphoid aggregates may be seen, reactive germinal centres are a relatively uncommon feature.[19 20] Hodgkin's disease is ruled out by the lack of the diagnostic Reed-Sternberg cells and atypical mononuclear cells. Vessels are prominent, but there is no true vasculitis nor are there malignant cytologic features, so that systemic vascular disease is unlikely.

Previously reported cases of periorbital Kimura's disease were successfully treated with excisional biopsy. Hidayat *et al*[6] reported excessive bleeding during surgery in one patient. Radiotherapy and intralesional steroids have not been tried in orbital disease. There has been some success with radiotherapy in skin disease.[6] In our patient the untreated lesions slowly increased in size and there was continuing eosinophilia but no other haematological abnormality. Despite the CT evidence of lateral rectus involvement eye movement was normal. This pattern suggests a low grade, possibly aberrant, hypersensitivity or allergic response to a continuing antigenic stimulus. We have compared the early and late pathological features in the eyelid over a 12 year period and found a continuing active inflammatory reaction but no evidence of neoplasia. Eosinophils were just as numerous in the late biopsy.

Surgical treatment of large eyelid nodules may present difficult technical problems. In one report an orbital lesion underwent severe haemorrhage on resection.[6] In such cases conservative management may be the best option, but should include biopsy and histopathological examination to rule out lymphoma.

In a large study of orbital and conjunctival lymphoid infiltrates, Medeiros and Harris[21] state that bilateral involvement and dissemination, such as cervical lymphadenopathy, at the time of presentation, occur only in lymphomas. Our case disproves this statement, showing the importance of histopathological examination.

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Progressive myopia in early onset chronic angle closure glaucoma

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Abstract

A 19-year-old girl presented with advanced unilateral chronic angle closure glaucoma and myopia with gross cupping and field loss in a previously hyperopic eye with a marked increase in corneal curvature. This emphasises that a marked myopic shift may be an important sign of glaucoma in a young patient.
(*Br J Ophthalmol* 1992; **76**: 758–759)

The possibility of missing a case of glaucoma which has caused the onset of myopia in a young patient is present in the minds of most ophthalmologists but usually it remains only a possibility and one seldom sees a case in clinical practice.

Recently, however, a case of unilateral chronic angle closure glaucoma (CACG) presented with unilateral high myopia with some interesting features and documentation.

Case report

A Caucasian female, presented aged 8 years. Uncorrected vision was right 6/12, left 6/18; refraction under mydriatic was right +3·0/−1·0 ×180° and left +5·5/−2·0×30° and the eyes were otherwise normal. At a final subjective test vision was equal, 6/9, with right +1·0/−1·0 ×180° and left −1·5×30°.

She returned, age 19 years, complaining of difficulty with some recent spectacles. She stated that she had obtained the glasses from an optometrist in the period since her last visit 11 years earlier and no further information was available regarding this period. Vision was now right 6/12 with −6·0/3·0×60° and left 6/9 with −1·0×150°. The anterior chamber depths were rather shallow, 2·4 mm right and left. There was no iridodonesis. The optic cup-disc ratios were right 0·8 with atrophy, left 0·4. The right visual field showed a large superior arcuate loss with Goldmann 2/IV, the left was full. Applanation pressures were right 38, left 20 mm Hg. The right angle was narrow with bowed iris and 50–90% closure by intermittent segments of peripheral anterior synechiae (PAS). The left angle was wide and open with moderate bowing of the iris and narrowed above. After bilateral YAG laser iridotomies the right angle was still closed above and intermittently elsewhere with 50–80% PAS. On pilocarpine hydrochloride and timolol maleate the IOP was right 25, left 12 mm Hg. After an uneventful right trabeculectomy IOP was right 8, left 12 mm Hg with a good drainage bleb. There was no change in anterior chamber depth or lens position following the instillation of pilocarpine.

On ultrasonography the anteroposterior lengths were right 21·1, left 20·7 mm with a normal lens thickness of 4·1 mm right and left. The posterior pole of the lens was 14·0 mm in front of the retina in the right eye and in the left eye the posterior pole of the lens was 13·6 mm in front of the retina. Corneal diameters were 12·0 mm right and left. Keratometric readings were right 54·0/51·5 axis 105°, left 45·5/49·1 axis 90°.

The patient was of normal height and build being 160 cm (5 ft 3 ins) tall with no brachydactyly.

Discussion

Angle closure glaucoma in myopia has been documented[1] with an incidence from 5·5% to 16·4%[2-4] and, though CACG is unusual in such a young patient, a number of cases have been reported.[5-9] The myopic shift in refraction in the right eye of the present case bears a marked similarity to the excessive loss of hyperopia in four young aphakic patients developing glaucoma described by Egbert and Kushner[10] who could not determine whether glaucoma or myopia was the primary process. In our patient unilateral myopia occurred in a previously known hyperopic eye with the development of CACG making it highly likely that the excessive myopic shift in refraction was secondary to the pressure rise.

The axial lengths of both eyes were short and almost equal in this patient so that the myopic shift in refraction in the affected eye was not due to the lengthening of the globe typical of high myopia. Further, though greater than expected for her age,[11] lens thickness was equal in each eye so that the unilateral myopia was unlikely to be lenticular in origin. An anterior shift of the lens in the right eye would explain the myopic shift if it were of sufficient magnitude. However the posterior pole of the lens in the right eye was only 0·4 mm more anterior to the retina than that of the left eye and would not explain a myopic shift of 6 dioptres.

The high keratometry readings (more than 2 standard deviations from the mean),[12] much higher in the more affected eye, indicated, therefore, that the increased refractive power was most likely to be corneal in origin, with a very highly curved cornea particularly in the right eye. It is noteworthy that this remarkable change in corneal curvature occurred though corneal diameters remained equal.

The glaucoma in this patient had some similarity to that which has been described in the Weill-Marchesani syndrome[13,14] with slight anterior dislocation of the lens and blockage of pupillary aqueous flow.[15,16] However this patient showed none of the physical features of the Weill-Marchesani syndrome, being of normal height and build, nor was there evidence of microspherophakia or dislocation of the lens into the anterior chamber.

The adolescent onset of CACG presenting with high myopia emphasises that an excessive myopic shift in refraction may occasionally be an important sign of the onset of glaucoma in a young patient.

In this patient an early onset of CACG at some time between 8 and 19 years was associated with a rise in IOP, an increase in corneal curvature in the affected eye and cupping and field loss. These changes were not accompanied by stretching of the sclera and lengthening of the globe. In the absence of any other likely explanation it seems probable that the raised IOP caused this sequence of events.

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British Journal of Ophthalmology 1992; 76: 760–761

Dermochondral corneal dystrophy (of François)

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Abstract

Dermochondral corneal dystrophy (of François) has been reported rarely in the literature. It consists of a triad of findings characterised by the development of skin nodules, acquired deformities of the extremities, and a corneal dystrophy. The corneal dystrophy is central and superficial with whitish subepithelial opacities. We present two brothers who display previously unreported ocular findings. Specifically, they developed confluent opacification of their central corneas with anterior stromal involvement, and peculiar anterior cortical cataracts. These findings should be added to the spectrum of findings seen in this rare disorder.

(*Br J Ophthalmol* 1992; **76**: 760–761)

Dermochondral corneal dystrophy is a rare familial disease initially described by François in 1949.[1 2] It consists of a triad of abnormalities affecting the bones of the extremities, the skin, and the cornea. We describe previously unreported ocular manifestations in a pair of brothers whose dermatologic findings were previously investigated.[3]

Case reports

Two Mexican brothers, aged 20 and 22½, with a history of dermochondral corneal dystrophy were referred for evaluation. Both had been born by spontaneous vaginal delivery and were healthy without abnormalities at birth. Four siblings are healthy and there is no history of consanguinity. As early as 9 months of age they began to develop nodules on their hands. Limb abnormalities and corneal findings were seen as early as age 3. The corneal opacities did not affect vision at that time. Histopathology of the skin lesions revealed 'spongiocytes' without staining by special lipid or mucopolysaccharide stains.[3] They have experienced a gradual decrease in visual acuity over the last several years. However, there is no history of ocular inflammatory episodes, and the patients have no history of redness, pain, or photophobia.

On ocular examination, the best visual acuity of the elder brother was 20/100 with both eyes and 20/80 in the younger brother. Their corneas showed numerous superficial and central corneal opacities which were white with irregular and blurred edges. Most opacities were subepithelial; some caused an elevation of the overlying epithelium. There was no breakdown of the corneal epithelium and there was no staining with fluorescein. The intervening cornea showed subepithelial and anterior stromal haziness (Fig 1). Gonioscopy revealed normal angle structures. Anterior cortical cataracts in a stellate pattern were evident (Fig 2). The rest of the examination was unremarkable.

Discussion

Dermochondral corneal dystrophy is a rare disorder with only nine cases having been reported in the literature.[1 3-7] Consanguinity was demonstrated in one case suggesting that transmission may be autosomal recessive.[4] This syndrome consists of a triad of findings which affects the bones of the extremities, the skin, and the cornea. There is an abnormal ossification of cartilage leading to abnormal skeletal development which is limited to the hands and feet. This leads to subluxations and retractions of tendons which gives rise to the deformities. The skin nodules look similar to xanthomas and involve the dorsal surface of joints of fingers, posterior surface of elbows, nose, and external ear (Figs 3, 4). Although the nodules appear to be xanthomatous they do not stain with lipid stains and probably represent a proliferation of anomalous fibroblasts.[7]

The ocular syndrome consists of a superficial and central corneal dystrophy with opacities of varying dimensions under the epithelium. The

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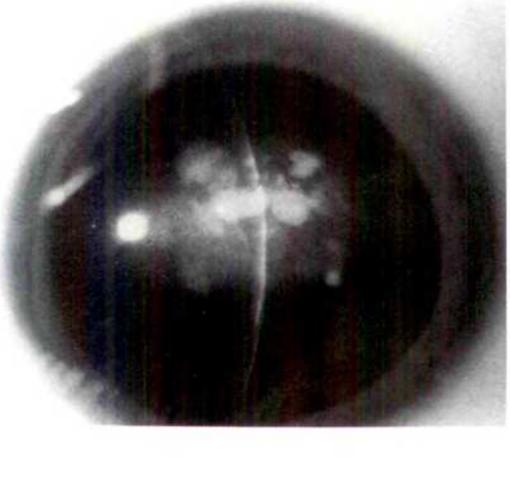

Figure 1 Slit-lamp photograph of the cornea. The large white opacities are subepithelial. There is haziness of the anterior third of the stroma.

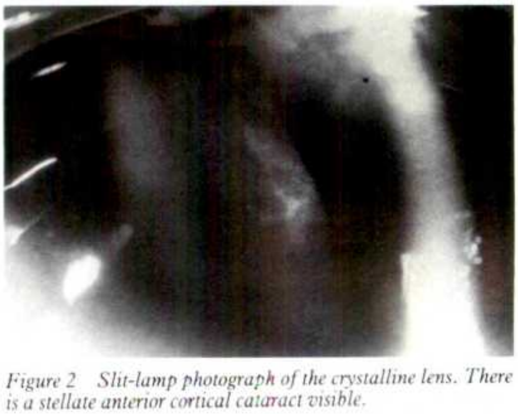

Figure 2 Slit-lamp photograph of the crystalline lens. There is a stellate anterior cortical cataract visible.

Figure 3 (A) Dermal nodules on the elbows in dermochondral corneal dystrophy. (B) Higher magnification of elbow nodules.

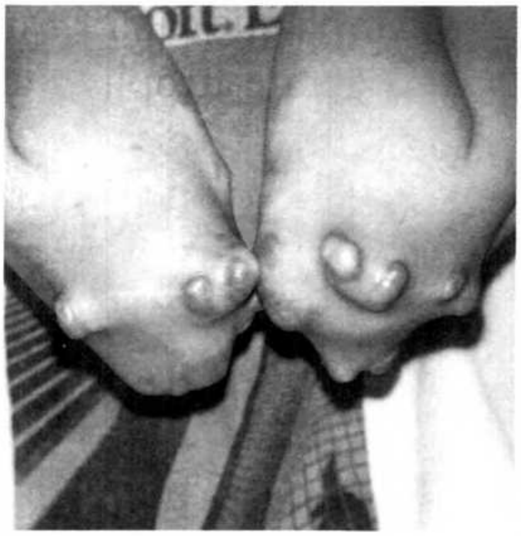

Fig 3A

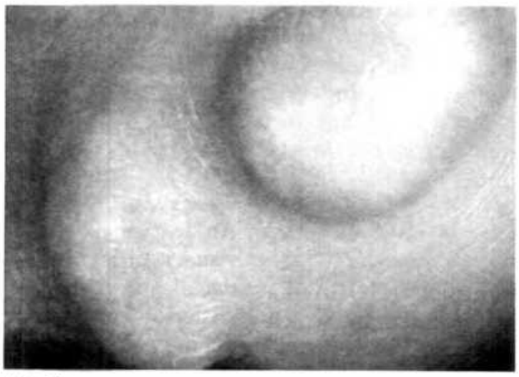

Fig 3B

opacities are white with irregular margins. In large opacities, there is elevation of the epithelial surface with an anterior convex wall, a posterior concave wall, and an optically empty space between them. The periphery of the cornea, the parenchyma, and the endothelium appear normal. Histological examination of François' cases showed an abnormal epithelium with Bowman's membrane being poorly defined and containing some histiocytes. The stromal tissue had scanty cells and cavities were evident.

The natural history of this syndrome is not clearly defined. François observed that his patients developed hand deformities between age 1 and 2, foot and skin abnormalities by age 5, and ocular abnormalities between age 8 and 9. Another case report suggested that the onset may develop later in life (age 33) in association with pregnancy and may also have gingival and conjunctival abnormalities. Analysis of collagen urinary metabolites in this case suggested there was a hyperproduction of type III collagen.[7]

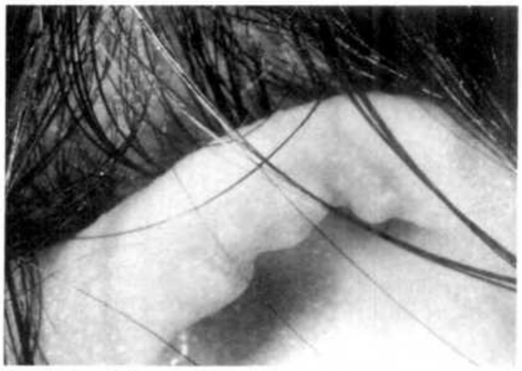

Figure 4 Nodules on the outer part of the ear in dermochondral corneal dystrophy.

By contrast, our patients had developed skin lesions in infancy, and limb and corneal abnormalities as early as age 3. Moreover, our patients developed anterior corneal stromal opacities, and cataracts which were previously unreported. These observations suggest that the ocular manifestations of this syndrome can be progressive and will probably require therapeutic intervention in the future.

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British Journal of Ophthalmology 1992; 76: 762–763

Anterior subcapsular plaque cataract in hyperornithinaemia gyrate atrophy – a case report

David Steel, Christopher M Wood, John Richardson, John McCarthy

Abstract

Hyperornithinaemia gyrate atrophy (HOGA) is a rare autosomal recessive disorder in which chorioretinal degeneration occurs with cataracts, myopia, and hyperornithinaemia. We report the case of an 18-year-old female who presented with the typical features of HOGA, including posterior subcapsular cataracts and elevated plasma ornithine. She later developed distorted vision in both eyes owing to wrinkling of the anterior lens capsules. Histological examination following lens extraction showed the wrinkling was caused by focal distortion from capsular fibrosis (anterior subcapsular plaque cataract). This specific lens change has not been linked previously with HOGA.

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Hyperornithinaemia gyrate atrophy (HOGA) is a rare autosomal recessive disorder in which chorioretinal degeneration occurs with cataracts, myopia, and hyperornithinaemia.[1] The ocular changes may be caused by either hyperornithinaemia or possibly hypoprolinaemia.[2] Two clinical subgroups have been described based on vitamin B6 responsiveness with vitamin B6 responsive patients having a less severe and more slowly progressive disease. We report a case which presented with posterior lens opacities typical of HOGA,[3] but later developed anterior subcapsular plaque cataracts bilaterally; a specific lens change which has not been previously linked with HOGA.

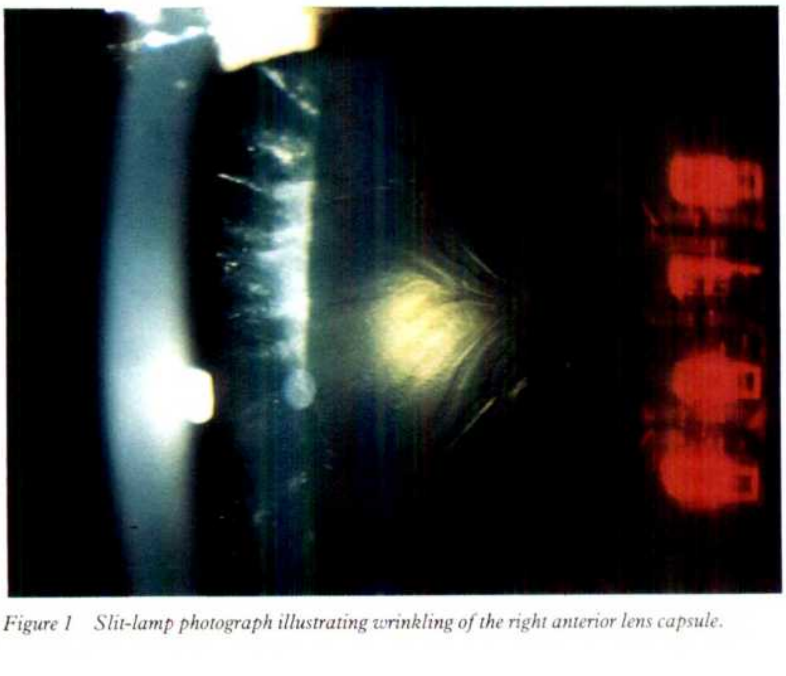

Figure 1 Slit-lamp photograph illustrating wrinkling of the right anterior lens capsule.

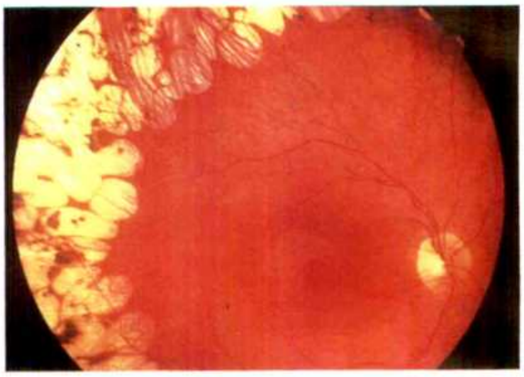

Figure 2 Fundus photograph illustrating gyrate atrophy of the retina and choroid.

Case report

An 18-year-old female presented with reduced visual acuities of 6/12 right and left. A presumptive diagnosis of HOGA was made on the basis of posterior subcapsular cataracts, myopia, confluent well circumscribed areas of peripheral chorioretinal degeneration, and a subnormal electroretinogram.

Ten years later she developed distorted vision in the right eye. Examination revealed visual acuities of 6/60 (6/18 with a pinhole) right, 6/18 left and a wrinkling of the right anterior lens capsule (Fig 1). The fundus changes in both eyes were typical of HOGA (Fig 2). Her own plasma ornithine was markedly elevated at 776 µmol/l, while her parents, brother, and daughter all had normal 24 hour urine and plasma ornithine levels.

Three months later the previously normal left anterior capsule became wrinkled. Histological examination following lens extractions showed extensive degenerative changes with formation of globular aggregates in the posterior sutural region and posterior migration of the lens epithelium to form a uniformly thickened 'double layer' posterior capsule.[3] The anterior capsule wrinkling was due to focal distortion from capsular fibrosis (anterior subcapsular plaque cataract). Her visual acuities have now improved to 6/12 in each eye.

Discussion

This patient illustrates all the typical features of HOGA, including the specific light and electron microscopic appearance reported in HOGA cataracts.[3] She had, in addition focal proliferation of epithelial cells to form anterior subcapsular cataracts. The only previous report of this type of cataract in HOGA concerned a postmortem study on an eye from an 89-year-old female with previous unspecified ocular trauma with the lens also being subluxated and hypermature.[4]

Wrinkling of the anterior capsule occurs in hypermature cataracts, and with capsule fibrosis initiated by anterior segment inflammation caused by trauma, surgery, uveitis, or atopy.[5] The lenses in our study developed anterior capsule wrinkling in the absence of any predisposing factors suggesting anterior subcapsular plaque may be another specific cataractous change associated with HOGA.

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British Journal of Ophthalmology 1992; **76**: 764–765

Pink hypopyon: a sign of *Serratia marcescens* endophthalmitis

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Abstract

Endogenous bacterial endophthalmitis in infants is uncommon. We recently examined and treated an infant who presented with pink hypopyon which followed a *Serratia marcescens* septicaemia. Culture of the aspirate from the anterior chamber showed no red blood cells, and grew *Serratia marcescens*, which was also isolated from the tip of the child's umbilical artery catheter. The presence of a pink hypopyon in the absence of hyphaema may suggest the diagnosis of *Serratia marcescens* endophthalmitis.

(*Br J Ophthalmol* 1992; **76**: 764–765)

Serratia marcescens, a Gram negative bacillus once believed to be a harmless saprophyte may cause infection in humans. This bacterium can cause meningitis, endocarditis, otitis media, sepsis, and ocular infections such as conjunctivitis and keratitis.[1-3] Endogenous bacterial endophthalmitis is uncommon but its occurrence in newborns has been reported.[2] We report a newborn infant who developed a pink hypopyon caused by *Serratia marcescens*.

Case report

After an uneventful pregnancy, a healthy 18-year-old primigravida had an uncomplicated labour and delivered a 2·65 kg full term infant. The neonate required resuscitation after delivery. Apgar scores were 1 at 5 minutes, 3 at 6 minutes, and 5 at 10 minutes. During the first few hours of life, the baby developed convulsions and was treated with 60% oxygen and phenobarbitone. Three days later the infant developed clinical signs of septicaemia and disseminated intravascular coagulopathy. *Serratia marcescens* was isolated from blood cultures and from the infant's ear, nose, and throat. *S marcescens* was also cultured from the tip of the child's umbilical artery catheter.

Ophthalmic examination disclosed a normal right eye. The left cornea was hazy centrally. A fibrinous exudate was seen in the anterior chamber occluding the pupil and precluding visualisation of the fundus. A pink hypopyon occupied one third of the anterior chamber. Ultrasound evaluation of the posterior segment revealed dense, dispersed vitreous opacities and retinochoroidal thickening consistent with endophthalmitis. No intraocular calcification was noted.

An anterior chamber paracentesis was performed. Gram stain of the aqueous specimen revealed Gram negative bacilli and polymorphonuclear cells. Haematoxylin and eosin stain of the fibrinous exudate showed polymorphonuclear leucocytes but not red blood cells. *Serratia marcescens* was isolated from the aqueous. Vitreous was aspirated for microscopy and culture. A 25 gauge needle on a tuberculin syringe was inserted through the pars plana at the 9 o'clock position and was advanced less than 1 cm to reach the mid vitreous. Liquefied vitreous (0·3 ml) was aspirated, and through the same site gentamicin 100 μg and cephazolin 100 μg were injected intravitreally. Culture of vitreous aspirate revealed no growth. The view of the fundus was not possible because of the hazy media.

Antibiotic sensitivity studies showed the organism to be susceptible to amikacin, chloramphenicol, carbenicillin, gentamicin, minocycline, and trimethoprim-sulphamethoxazole, and resistant to ampicillin, cephalosporins, erythromycin, polymyxin B, and tetracycline. Radiological examination of the extremities confirmed the presence of periosteal reaction suggestive of osteomyelitis. The patient responded to parenteral gentamicin therapy. The left eye showed progressive healing of the inflammatory reaction. Three months later the left eye started showing evidence of phthisis.

Discussion

Serratia marcescens was first described by Bizio in 1823.[4] Subsequently, the bacterium became known as *Bacterium prodigiosum* because it produces a red pigment (prodigiosin). Its red pigment has been a useful marker in the study of bacteraemia after dental extractions[5] and bacteriuria after urinary tract procedures.[6] *S marcescens* endophthalmitis has rarely been reported. A review of 72 cases of metastatic endophthalmitis in the past 10 years disclosed only three cases of *S marcescens*, all in the adult age group.[7-9]

Endophthalmitis in infants has received little attention. Three cases of bacterial endophthalmitis reported in the neonatal age group were reported to have been caused by *Streptococcus pneumoniae*, *Streptococcus algalactiae*, and group B *Streptococcus*.[10-12]

Serratia marcescens ocular infections have been described as purulent conjunctivitis in six premature infants.[13] In 1971 Bigger *et al* reported two cases of severe purulent endophthalmitis owing to *S marcescens* in adults.[14] We assume that our patient had metastatic endophthalmitis following septicaemia acquired by umbilical artery catheter infection.

Because of the potential severity of ocular involvement by this organism, a characteristic presentation of pink hypopyon may suggest *S marcescens* and should prompt the ophthalmologist to look for laboratory confirmation and institute immediate management with appropriate antibiotics such as gentamicin.

Endogenous metastatic endophthalmitis in infants is rare. Vitrectomy and intraocular antibiotic injections may be indicated in such patients but are technically demanding if the view is obstructed, and may carry considerable risks.

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LETTERS TO THE EDITOR

Severe intraocular infection: complications of β irradiation induced scleral necrosis following pterygium removal

EDITOR,—It was with interest that we read Dr Plowman's excellent article in your journal recently.[1] We would like to raise one important point, however. The author states that pterygia respond well to radiotherapy; however, our experience in Australia, where this condition is more common, suggests that following such treatment, there are recurrence rates of 20%.[2]

Tarr and Constable[3] highlighted the potential hazards of scleral necrosis following β irradiation with strontium plaques. Since then the practice in western Australia has been to limit the number of treatments, but even with doses as low as 800–1600 cGy we have had 12 severe cases of intraocular infection over the past 5 years referred to our institution. The condition may remain undiagnosed or masquerade as marginal keratitis, herpetic disease, posterior scleritis, or serous retinal detachment for some time. *Pseudomonas*, *Streptococcus* and *Candida* are commonly implicated, but rare ocular pathogens such as *Petriellidium boydii* and *Scedosporium inflatum* may be causative. Visual handicap is severe and only one patient has retained good visual acuity, with one patient requiring enucleation. Generally the ocular complications have been devastating.[4]

Typically a long latency between radiotherapy and ocular sepsis occurs (usually 15–20 years) and removal of calcific plaques at the base of the ulcer commonly precipitates sepsis.[4]

We no longer employ radiotherapy following removal of pterygia. In our institution last year we treated 114 patients with pterygia and there is no doubt that conjunctival autografting is our treatment of choice to reduce recurrences.

Though the incidence of pterygia is low in temperate latitudes,[5] an increasing migrant and itinerant population may mean more consultations for pterygia will occur in the United Kingdom. If radiotherapy is to be used at all, we would stress the necessity for limited treatment, and only in skilled hands dealing frequently with this mode of therapy, to avoid these devastating sequelae.

ANTHONY P MORIARTY
GEOFFREY J CRAWFORD
IAN L McALLISTER
I J CONSTABLE
Royal Perth Hospital,
Department of Ophthalmology,
Perth, Western Australia

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Reply

EDITOR,—The Royal Perth Hospital experience with complications from β irradiation of resected pterygia is of great interest as it is at marked variance with our own, using higher doses with strontium plaques after excision of conjunctival tumours. Actinic changes in the conjunctiva contribute to the development of pterygia. Is it possible that this prior damage is the major factor in the development of postoperative complications rather than the radiation dose prescribed?

P N PLOWMAN
J L HUNGERFORD
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BOOK REVIEWS

Repair and Reconstruction in the Orbital Region. 3rd edn. Edited by JC Mustardé. Pp 566. £95.00. Churchill Livingstone: Edinburgh, 1990.

This book contains a wealth of detail and it must serve both to stimulate any interested ophthalmic surgeon and to enrich the experience of those surgeons already involved in periorbital reconstruction. The gift of lucid teaching, so characteristic of Mr Jack Mustardé, is evident throughout the work; the basic anatomy and physiology of tissues, especially the eyelids, is applied throughout to the problems of oculoplastic surgery.

After introducing the concepts of eyelid structure and function, the repair of partial thickness eyelid lesions is dealt with in a logical sequence – the primary repair, secondary complications and treatment, loss of superficial or deep tissues, and the loss of conjunctiva. The text then covers the primary and secondary repair of full thickness defects of the eyelids and periorbital tissues. Most of the techniques available for reconstruction of the upper, lower, or both eyelids are clearly described and the merits and disadvantages of each method are discussed in detail. The systematic approach is completed by two chapters about reconstruction surgery of the medial and lateral canthi.

The second part of the book deals with the management of various groups of ophthalmic conditions or particular aspects of reconstructive surgery. It contains chapters by co-authors of the highest international standing – lacrimal disease (Welham), socket surgery (Vistnes), craniofacial malformations and trauma (Jackson), eyelid malpositions (Collin), and ptosis (Beard). Other chapters, by Mr Mustardé, cover eyebrow reconstruction, congenital and acquired anophthalmos, some aspects of ptosis, medial canthal anomalies, colobomas, exenteration, and also practical details for the harvesting of tissue grafts.

It is evident throughout that the surgical techniques have been evaluated thoroughly and much practical advice is given; this advice also includes examples of techniques which should be avoided! There are a large number of excellent illustrations which complement the text and demonstrate the efficacy of the methods presented.

The book is of the highest quality, well bound, and has only a handful of minor errors. Though some of the more recently introduced surgical methods are not described there can be no doubt that it is an essential reference text for surgeons who deal with periorbital reconstruction; the clarity of ideas and the detail in this work will delight this group. Browsing through such a well-written and beautifully illustrated work, however, will benefit any ophthalmologist or other medical practitioner.

GEOFFREY E ROSE

Night Vision: Basic, Clinical and Applied Aspects. Edited by R F Hess, L T Sharpe, K Nordby. Pp 550. £65. Cambridge University Press: Cambridge, 1990.

This volume provides a welcome overview of human scotopic visual function at a time when major advances are being made in understanding the underlying mechanisms of loss of night vision in retinitis pigmentosa and other retinal dystrophies which can selectively target rod mediated vision. In their preface the editors note Sir Stewart Duke-Elder's praise of the previous resumé of work about night vision. The same praise could be expressed for this work which succeeds in bringing together biochemistry, electrophysiology, and psychophysics in an intellectually challenging field.

The chapters are uniformly of high standard and cover basic mechanisms from the rod photoreceptor, photochemistry, receptor physiology, five detailed chapters about the important findings in that rare condition of achromatopsia (based heavily on extensive investigations of the visual function of one of the editors), to clinical aspects and mainly theoretical and research aspects of night vision devices.

One of the strengths of a collection like this is that it provides a forum for leading scientists to discuss issues in greater depth, revealing areas where clinicians can apply new basic research findings to interpreting physiological mechanisms of disease. Particularly interesting in this respect is the chapter on dark adaptation by Lamb where he re-examines the classical thinking about the role of bleached rhodopsin and neural mechanisms in adaptation. For those clinicians who are interested in age-related macular degeneration, where abnormalities of dark adaptation have been found, this provides important clues to understanding potential mechanisms. In addition since in retinitis pigmentosa the molecular biological findings of abnormalities in rhodopsin are now being discovered, we can begin to consider how these changes in the structure of the molecule result in the loss of function. These highly selective changes in retinitis pigmentosa (often single amino acid substitutions) with their devastating visual consequences provide important models for understanding the underlying physiology and this chapter discusses relevant considerations.

The chapter about clinical manifestations gives an excellent introduction to this aspect of night vision and would perhaps better be read before the other chapters by clinicians. It explains clearly the importance of considering underlying physiological mechanisms as well as putting in perspective the issue of selectivity and the potential these conditions have for furthering our understanding of normal vision. This chapter necessarily omits reference to the latest molecular biological findings since it was written before these were known and it will be exciting to see these included in the next resumé of night vision when the recent results in this fast moving field can be incorporated.

In summary, this volume provides excellent background on the physiology and psychophysics of night vision. It will be of interest to vision scientists and basic researchers studying human night vision as well as clinicians curious about the underlying physiology of visual function abnormalities.

F W FITZKE

Current Concepts of Multifocal Intraocular Lenses. Edited by Andrew Maxwell, Lee T Nordan. Pp 240. £49.00. Slack: Beckenham, Kent, 1991.

The development of bifocal and multifocal intraocular lenses is a natural one but strangely has arrived on the intraocular lens scene late. This book reviews the conceptual development of multifocal lenses sometimes in a rather anecdotal way but includes the benefits derived from spectacle and contact lens multifocal styles. The design of the anullar, bull's eye, and difraction grating type lenses is adequately covered and there is a passing reference to a split 'executive style' bifocal lens which would be more common in spectacle lenses.

The material overall is presented by an inspiring list of contributors. In the early chapters there are basic optics with much ray tracing and even wave front reconstruction to show how both refraction and diffraction lead to the image on the retina. These techniques are used to produce focus spot diagrams calculated for single fixed objects in a series of image planes at different distances from the lens. Thus the image quality for monofocal, bifocal, and multifocal intraocular lenses is derived. These spot diagrams are very revealing as to the quality of image that can be projected onto the retina from these various types of lenses and on the problems associated with them, such as tilt and decentration.

New optical and mathematical tools are brought to bear on the problem such as modulation transfer function in which image contrast is expressed as a fraction of object contrast and this function is plotted against line resolution, the resulting transfer function being of value to lens designers and users alike. Sound physical optics are used throughout the book.

All currently available types of multifocal lenses are discussed, including some not in very wide use such as the Nordan aspheric lens and the AMO Array multifocal intraocular lens, in which the entire refractive sequence is repeated in each of five relatively narrow zones. Zone plate lenses such as the 3M bifocal are discussed, but much less familiar to readers will be the phase plate lenses. All of these types are related to their diffraction limiting characteristics and the spot diagrams also form a measure of image transfer including aberration induced by off axis spots, tilt, and decentration.

The role of retinal imaging in processing and cleaning up the spurious parts of the spot diagrams is explored extensively and it is suggested that filtering of retinal noise by raising the threshold and by inhibition and coincidence may provide a gating mechanism which improves retina to brain transfer. There are extensive, essential discussions of decentration and tilt of almost all the lens styles. There is the suggestion that diffraction and Array type lenses may avoid these problems.

While the book is generally a supportive thesis for multifocal lenses, there is some balance provided in chapter 18 where Steve Charles and Paul Runge suggest disadvantages in relation to examination of the retina and internal vitreoretinal procedures. They also indicate reduced visual function where the light and contrast losing possibilities of multifocal lenses may be accentuated by co-existing retinal or macular disease.

The later chapters relate to iatrogenic and preoperative astigmatic control and to arguments of capsular bag and sulcus placement. These are to some extent repetitive of material published elsewhere, especially in the *Journal of Implant and Refractive Surgery*. Much the same could be said of the chapter on A scan examination, although it is still worth reading.

In summary, this book is very useful for those who implant multifocal intraocular lenses. Others who choose not to may also find that it contains much theoretical information of value for all implant surgeons and for technicians involved in the support services for implantation.

C G F MUNTON

Moving to Audit – An Education Package for Hospital Doctors and General Practitioners. By Centre for Medical Education, Ninewells Hospital and Medical School, Dundee. Pp 128. Complete package (resource book and challenge pamphlets) £29; resource book only £12.50+£1.50 pp. Postgraduate Office, Ninewells Hospital and Medical School: Dundee, 1992.

In response to the increasing demand for doctors to become involved in medical audit, the Centre for Medical Education in Dundee has produced a distance learning programme aimed at both hospital doctors and general practitioners. The package is based upon a reference book, clearly and concisely written, which explains what audit is and is not, the potential benefits to be derived from medical audit, and how to initiate an audit programme within one's own practice.

While the initial sections of the book are likely to be useful to those who are sceptical about the benefits of audit, or completely ignorant of the concept, those who have already embarked upon some form of audit exercise may find themselves very familiar with much of the material in the first four chapters. The remaining two thirds of the book covers techniques used in taking samples of a population, how to collect, store, and handle data, and an elegantly straightforward section on basic statistical analysis. The level at which the book is pitched is probably right for most hospital doctors who are just beginning to familiarise themselves with the audit process, but each chapter contains valuable guidance on further reading.

The other components of the package are sets of questions, both multiple choice and brief written exercises, which come in two versions: one for hospital doctors and the other for general practitioners. They are designed to be used in conjunction with the reference book to make the participants think critically about the way in which they can implement or improve on their use of audit in their own practice and encourage their involvement in initiating audit. The responses to these exercises can be forwarded to the Centre for Medical Education, Dundee and guidance is then given as to how the participants' answers compare with those of other doctors involved in the programme. New exercises are dispatched at regular intervals to maintain continuing interest.

This package appears to have been well designed and produced and should provide a very useful introduction to those wishing to become involved in medical audit. It should assist them in carrying out meaningful work while avoiding many potential pitfalls and errors and help to maintain their enthusiasm for continuing critical analysis of their working practices.

COLIN HUTCHINSON

Collecting Ophthalmic Antiques. By Ronald J S Macgregor. Pp 56. £3.75. The Ophthalmic Antiques International Collectors' Club: Saltcoats, Ayrshire, 1992.

This excellent little handbook is a mine of information.

It is designed basically for the beginner in ophthalmic antique collection, but is so full of hints and wrinkles that anyone starting to shop for old items, in any field, will derive benefit, and gain tips on how to set about commencing their collection.

What appears to be a simple topic is soon expanded by the author, as he narrates the width of subspecialties within the subject. Thus one's fancy may be drawn towards spectacles or ophthalmic instruments at one end of the spectrum to eyebaths, books, and optical toys at the other.

The booklet ends with advice on the care and display of items, and there is a reference to museum collections worldwide, together with a list of market places and auction houses.

The author is to be congratulated on producing a stimulating, readable book, which will set the informed readers exploring their waste bins, and sallying forth into the highways and byways for hidden treasure of historic interest, and who knows, perhaps some value as well.

G V CATFORD

Books received

Blind and partially sighted children in Britain: the RNIB survey. Volume 2. By Errol Walker, Michael Tobin, Aubrey McKennell. Pp 292. £19.95. HMSO: London, 1992.

Fundamentals of Ophthalmic Practice. By S A Kamenetzky. Pp 150. $50. Raven Press: New York, 1992. (Available from Gower Medical Publishing: London.)

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (Mastercard, Visa, or American Express), stating card number, expiry date, and full name.

OBITUARY

T D V SWINSCOW DSC, MSC, MB, BS

Contributors to and readers of the *British Journal of Ophthalmology* will be sorry to hear of the death of Dr T D V Swinscow who was our technical editor from 1977 until 1991.

'Dougal' Swinscow was a scholarly man of small physical stature and unassuming manner, possessed of great charm and a gentle wit, but an eagle eye for grammatical errors, unsubstantiated claims, faulty statistics, obfuscation, and humbug upon all of which, and any other irregularities which in his view rendered a paper less than fit for publication, he would pounce with firmness but unfailing

courtesy. He never ceased to marvel at the extensive selection of mistakes and cock ups together with infractions of the laws of science and syntax which would be contributors contrived to include in their submissions. Many former authors (professors included) will doubtless remember his polite enquiries as to why certain numbers did not add up, why Figure 3 was not referred to in the text whereas another figure which *was* referred to in the text was missing, why certain passages were repeated several times in the same paper, and (a particular bête noire of his) why the pages were not numbered.

As a guide, philosopher, and friend to the scientific editor he was invaluable, not only because of his scientific and literary attributes but also because of his long experience in medical journalism from the political and legal points of view; he could spot an attempted scientific fraud or a potential copyright dispute a mile off and was always available as a steadying influence with fractious would be authors with grievances.

Thomas Douglas Victor Swinscow was born on 10 July 1917. He was educated at Kelly College, Tavistock, and St Thomas' Hospital Medical School, London, qualifying in 1940. He was soon in the RAMC, serving first in the North African campaign and later in Europe in the 1st Airborne Division. He took part in the battle of Arnhem where he was hit in the back by two bullets while saving a wounded man. He survived many attempts by the enemy to kill him, including one episode where mortar shells, aimed at him personally, fell to his right, to his left, in front, and behind, but after these apparent ranging shots the ammunition fortunately appeared to have run out. He escaped across the Rhine with the rearguard but would only leave the wounded (in someone else's hands) when ordered to do so.

After the war he joined the staff of the *British Medical Journal* where he rose to the position of deputy editor. On his retirement from this full time post he took on the task of technical editorship of several of the special journals, but eventually settled for the *BJO* alone.

Dougal Swinscow was a man of unusual versatility. As well as his editorial activities he found time to become a world authority on lichens, founding the British Lichen Society and its journal *The Lichenologist*, and writing a textbook *The Lichens of East Africa*. On top of this he was an authority on medical statistics, his textbook *Statistics at Square One* selling around 100 000 copies; he published poetry in a journal run by T S Elliot, was an expert on the history and design of gardens, and combined this interest with his lifelong devotion to the Taoist way in his beautiful work *The Mystic Garden*, completed in a race against time with his final illness. He also wrote a fascinating autobiography, *Reap a Destiny – Divagations of a Taoist*, in which his colourful life and that of his slightly eccentric family background (his mother was a crack pistol shot and a heavy pipe smoker), are beautifully described.

He died on 24 September 1992 aged 75 and is survived by his devoted wife Josephine and three daughters.

REDMOND SMITH

NOTES

Congress of the Ophthalmological Society of Southern Africa

The OSSA congress will be held on 14–18 February 1993 at Arthur's Seat Hotel, Sea Point, Cape Town. Further details: Mrs Sally Elliott, Postgraduate Medical Centre, UCT Medical School, Observatory 7925, Cape Town, South Africa. (Tel: (021) 47–1250, ext 381; Fax: (021) 448–6263.)

Cataract '93

A joint meeting of the 4th International Cataract Epidemiology Meeting and 6th Scheimpflug Club Meeting, dealing with the epidemiology of cataract in its broadest sense and in techniques for imaging and analysing the anterior segment of the eye will be held in Melbourne, Australia, from 6–12 March 1993. Further information: Secretariat, Melbourne University Department of Ophthalmology, 32 Gisborne Street, East Melbourne, Victoria, 3002, Australia. (Fax: +61–3–662.3859.)

European Congress on Ambulatory Surgery

The 2nd European Congress on Ambulatory Surgery will be held in Brussels on 19 and 20 March 1993. Further details: Dr Cl De Lathouwer, Brussels One Day Clinic, Avenue du Duc Jean 71–73, B-1080 Brussels, Belgium. (Tel: +322/424 1212; Fax: +322/425 7076.)

Joseph F Morgan Research Foundation

The Joseph F Morgan Research Foundation, with the support of Health Protection Branch, Health and Welfare Canada and the Canadian Council on Animal Care, is holding an international symposium entitled 'Current trends: in vitro skin toxicology and eye irritancy testing' on 21–23 April 1993 at the Radisson Hotel, Ottawa Centre, Ottawa, Ontario, Canada. Further details: Vicki Nash-Moore, Symposium Coordinator, Golden Planners Inc, 126 York Street, Suite 404, Ottawa, Ontario K1N 5T5, Canada. (Tel: (613) 594–8226; Fax: (613) 565–2173.)

Master's Degree Programme in Public Health Ophthalmology

A special master's degree programme in public health specialising in preventive ophthalmology will again be offered during the 1993–1994 academic year by the Johns Hopkins Medical Institutions under the auspices of the Dana Center for Preventive Ophthalmology (a World Health Organisation Collaborating Centre). The programme is designed for individuals with ophthalmic experience or training interested in initiating, developing, and providing leadership to national or regional blindness prevention activities and in conducting serious clinical epidemiological research. Ten places are available for participants from developing and developed countries. A small stipend awarded on a competitive basis may be available to a limited number of participants to help defray living expenses. For further information: Program Coordinator, Preventive Ophthalmology Program, DCPO, Wilmer Institute Room 116, Johns Hopkins Hospital, 600 N Wolfe Street, Baltimore, MA 21205, USA.

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THE YEAR OF COMPLIANCE

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